CHAPTER XIV

FUNGOUS INFECTIONS OR MYCOSES

By FREDERIC M HAYES

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INTRODUCTION

Although fungi are of universal occurrence and frequently invade the body often producing serious lesions study of these organisms has been neglected by both clinicians and routine laboratory workers It may be mentioned as an example of the great importance of fungous infections that one half of the population of the United States is said to have the skin disease known as athlete s foot caused by a trichophyton or epidermophyton The local invasion and growth of such dermatophytes (Fig 2) not infrequently produce what is believed to be an allergic condition of the skin which results in generalized reactions to the fungus or its products Widespread eruptions of various types occur (Fig 3) accompanied by anorexia fever general adenopathy and leukocytosis Such reactions called *dermatophytids* can be induced by the subcutaneous injection of an extract of the fungus into a hypersensitive patient

THALLOPHYTA

SIMPLE VEGETATIVE STRUCTURES
NOT DIFFERENTIATED INTO ROOTS, STEMS OR LEAVES

ALGAE
CONTAIN CHLOROPHYLL
SYNTHESIZE FOOD

FUNGI
DO NOT CONTAIN CHLOROPHYLL
ARE PARASITIC OR SAPROPHYTIC

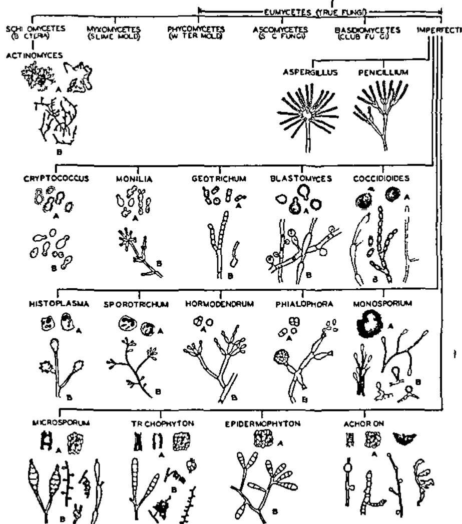


Fig 1 This schematic representation by Dr Norman F Conant of some of the pathogenic fungi shows (A) their microscopic appearance *as they occur in the tissues and* (B) as they are seen microscopically in cultures

The molds yeasts and actinomycetes are fungi non chlorophyll containing organisms which grow in irregular plant masses and are not differentiated into roots stems and leaves like higher plants Such a plant mass is called a *thallus* and plants which grow in this fashion are classified as *Thallophyta* (Fig 1) The fungi are subdivided into the true fungi or *Eumycetes*, the bacteria or *Schizomycetes* and the slime molds or *Myxomycetes* The ray fungi or actinomycetes represent a transition form between bacteria and molds

Fungi being devoid of chlorophyll cannot metabolize food from inorganic compounds but must depend upon previously synthesized organic matter, thus living either as saprophytes or parasites Some fungi like yeasts are unicellular but most are multicellular the cells being arranged end to-end to form filaments or hyphae which branch and intertwine to form a tissue called a mycelium From such a mycelial mass which serves to nourish the plant certain filaments extend into the air as aerial hyphae and some of these forms become specialized and discharge spores Such spores can give rise to a new mycelium by germination

Fungi were recognized as producers of disease in both plants and animals long before the discovery of the anthrax bacillus which was the first bacterium shown to bear a specific relationship to an infectious disease Pasteur s sensational discoveries were received with such scientific enthusiasm that as a consequence the study of pathogenic fungi suffered great neglect and it was only after the publication in 1910 of Sabouraud s work on the fungi that medical mycology again attracted a significant number of workers

A convenient and sufficiently accurate clinical classification can be made by separating the superficial or cutaneous dermatophytoses from the deep or systemic mycoses The superficial mycoses are described in textbooks of dermatology and of the deep mycoses only ten need be considered in detail in a text designed for internists

A clinic that does not have access to the opinion of a trained mycologist will surely fail to demonstrate the cause of many obscure infections Since pathogenic fungi may affect any tissue in the body the possibility of mycosis should be considered in the differential diagnosis of all unexplained infections That this is not always done is apparent from the number of patients suffering from a pulmonary mycotic infection who are sent to sanitoria with the erroneous diagnosis of tuberculosis

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FIG 2 Dermatophytosis of the feet (athlete's foot)

PATHOLOGY

Wherever fungi invade the body there results the usual tissue changes seen in chronic granulomatous inflammations such as caused by many varieties of bacteria. Microscopically the tissue changes are those of a foreign body reaction with giant cells, necrosis and fibrosis, and often it is difficult to distinguish the granulomatous changes produced by fungous invasion from those due to tuberculous infection. When secondary bacterial invasion occurs, as it often does especially in skin lesions, there is the superimposed picture usually encountered in pyogenic infection.

Unless the causative fungus can be demonstrated in the granulomatous tissue, pathological studies are of very slight aid in diagnosis. Careful and repeated studies, where necessary, of purulent discharges from sinuses or of material obtained by curettage is the most helpful method of establishing the diagnosis of fungous infections.

The technic for the demonstration of fungi in the skin, sputum or purulent exudates is not difficult. Material such as hair, skin or nail scrapings may be examined microscopically after a preliminary treatment with 10 to 20 per cent potassium hydroxide. The preparations are made by putting a small piece of the material to be examined in a drop of potassium hydroxide on a slide and covering the preparation with a cover glass. By gently heating the slide over a low flame the preparation is cleared almost immediately, and the fungi, if present, are seen readily.

Pus, exudates and sputum may be examined fresh or with 10 per cent potassium hydroxide added to the material. If the condenser of the microscope is lowered when fresh material is examined, the fungous structures are seen more readily. Since the fungi retain the stain when treated by Gram's method, fresh material should be examined also with this stain, especially in cases of moniliasis and actinomycosis.

For the most part fungi are cultured easily on the routine media used in laboratories of bacteriology. If hair, skin or nail scrapings are collected and kept between sterile slides for a week, small pieces of the material may be planted on Sabouraud's glucose agar slants, maintained at room temperature, and cultures obtained. Sputum, pus and biopsy material should be streaked on slants of Sabouraud's media and on blood agar plates and slants, which should be grown at both room and incubator temperature.

An enriched medium and anaerobic conditions are necessary for the cultivation of *Actinomyces bovis*; glucose ascitic fluid agar and Loeffler's medium give good growth if the source of material is relatively free from bacterial contaminants. *Cultures for fungi should not be discarded and reported as negative in less than a month, as many of them grow very slowly.*

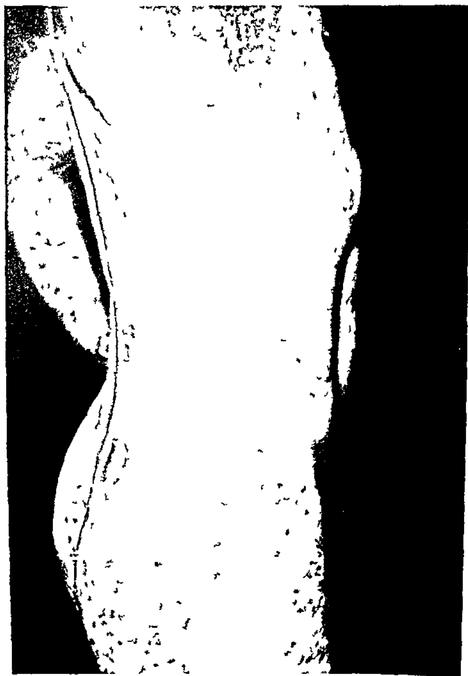


Fig. 3. Generalized skin eruption or dermatophytid of the patient whose feet are shown in Fig. 2.

Treatment

All general measures such as an abundant well balanced diet rest and good nursing care will be needed for the deep or systemic types of fungous infections which pursue as a rule a long chronic course Treatment must be individualized and some or all of the following therapeutic measures may be employed

Surgical drainage should be employed where needed and possible but meddlesome surgery may do much harm by spreading the infection *It is wise to precede* any surgical interference with a course of sulfonamide treatment bringing the blood level to from 5 to 10 mgm per 100 c c Such precautions should be applied also to curettage for diagnostic purposes It is still unproved that the sulfonamide drugs are fungicidal though good results have been reported especially in the treatment of actinomycosis They are of aid in controlling secondary infection and should be used with the usual precautions

Gentian violet in 1 per cent solution in 10 per cent alcohol is very useful in the treatment of superficial suppurating lesions It is especially valuable in *treating the lesions of moniliasis The stimulating effect of x rays on old fibrotic* lesions may aid resolution

Several recent reports indicate that penicillin is of value in actinomycosis but much more experience with the drug must accumulate before a positive judgment can be formed There is no objection to combining sulfonamide and penicillin therapy with the intensive use of the iodides

Vaccines are useful for desensitization where an allergic state exists and they have been used with varying success in treatment

Since Gilchrist s successful use of the iodides in the treatment of blastomycosis *the use of these drugs has been the most reliable therapeutic measure available*

Potassium iodide in saturated solution is measured by drops and is administered orally in 30 c c of water In the slow method 3 drops are given three times a day after meals and the dose increased daily by 1 drop per day (not 1 drop per dose) until the patient is receiving 20 drops three times a day The dose then is reduced to the starting point of 3 drops and increased again to the maximum of [illegible] drops three times a day

By the rapid method the initial dose is 5 drops three times a day after meals and the dose is increased by 1 drop for each dose or 3 drops each day The drug may be stopped *when a dose of [illegible] drops three times a day is reached or it may* be increased to as much as 100 drops three times a day If symptoms of iodism appear the drug should be discontinued until the symptoms have disappeared and treatment resumed beginning with 5 drops three times a day Such courses of treatment by either the slow or the rapid method should be continued for months and in some cases for years

Sodium iodide intravenously in daily doses of 1 gm may be used to supplement or substitute for the potassium iodide

' *Ethyl iodide* inhalations have been employed successfully in some cases of actinomycosis and blastomycosis the drug being administered *with an inhaler* of the type made by the Warren Collins Instrument Company of Boston, Mass The initial dose, measured in the graduated centrifuge tube attached to the instrument should be 0 25 c c three times a day This may be increased by 0 25 c c three times a day every 3 or 4 days until the patient is taking as much as 1 c c three times a day The inhalation treatment may be combined with the oral administration of potassium iodide

The action of iodide on inflammation and diseased tissue is imperfectly understood The halide is said to have a histolytic effect' and to aid in the reabsorption of inflammatory lesions In tertiary syphilis the ion provokes a favorable reaction leading to the resolution of gummatous tissue This may be a response to some type of irritation to which pathological tissue is unusually susceptible For example in tuberculous patients iodides arouse irritative reactions *and may even activate a dormant lesion In tuberculous patients therefore* iodides are contraindicated

Actinomycosis

Etiology — This is the commonest of the deep or systemic mycoses and often is a serious menace to life It is caused by the ray fungus *Actinomyces bovis* which usually gains entrance to the body through the buccal cavity and then may infect secondarily the deep tissues of the neck the lungs and the alimentary tract *Actinomyces bovis* has not been found in nature It has been cultured from the buccal cavity around carious teeth and from the tonsils of apparently healthy persons which indicates that the source of infection usually is endogenous The skin may be infected directly from abrasions but much more often it is invaded from lesions originating within the mouth and extending outward through the subcutaneous tissue It has been stated frequently that agricultural laborers are infected more often than other classes of workers but this may well be due to poor oral hygiene No age is exempt but the disease is commonest between the ages of 15 and 35 Twice as many males are affected as females

Symptomatology — The site of infection determines largely the clinical picture In 56 8 per cent of the reported cases the lesions were of the cervicofacial type affecting primarily the head and neck In the remainder the first lesions were in the lungs and thoracic cavity in 15 per cent in the abdomen in 22 3 per cent and in 5 9 per cent isolated lesions were found in other parts of the body

Cervicofacial actinomycosis is the commonest form of the disease and from a primary focus in the buccal cavity the infection may spread to the nasal sinuses to the salivary glands to the orbit and to the deep tissues of the neck or mediasti



FIG 4 Cervicofacial type of actinomycosis The brawny indurated tumor is perforated by draining sinuses

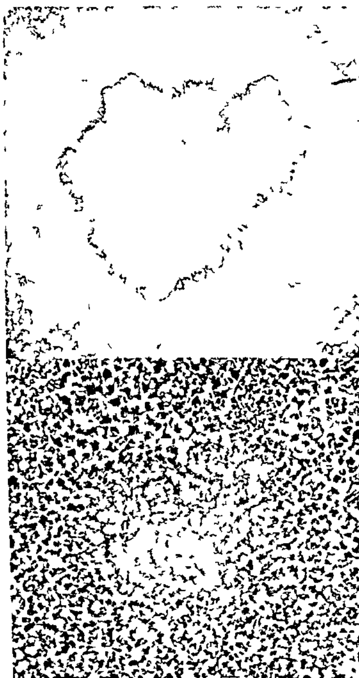


FIG 5 *Actinomyces bovis* Above sulphur granule with clubs as seen in pus *Below* a granule without clubs in pus Magnification 450

num Firm nodules single or multiple appear in the submaxillary region and as such nodules increase in size the skin over them changes to a dusky red or violaceous hue By this time other nodules usually have formed and one by one they break down resulting in fistulous ulcerations which discharge purulent material The skin assumes a ligneous hardness and in the end presents the appearance of a chronically inflamed mass riddled with intercommunicating sinuses (Fig 4)

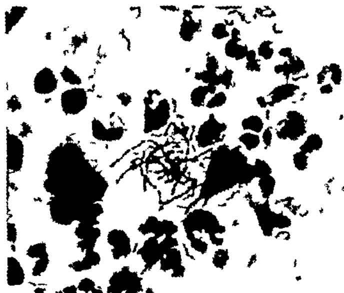


Fig. 4 *Actinomyces bovis* Branching gram positive filaments seen when a sulphur granule is crushed and stained by Gram's method Magnification 1300

Thoracic actinomycosis — The early symptoms are those of a subacute pulmonary infection with cough fever and some expectoration which gradually becomes mucopurulent and may contain blood Small abscesses form in the lung frequently involving the pleura causing pain The chest wall is invaded and sinuses develop As the infection progresses the patient becomes anemic loses weight and strength and frequently has a spiking temperature with night sweats and dyspnea The fungus may invade the mediastinum pericardium and heart

The physical findings in the early stages resemble those of tuberculosis and may lead to a mistaken diagnosis As the disease progresses massive areas of dullness appear usually at the bases and chest films reveal areas of consolidation containing small ill-defined patches of rarefaction suggesting abscesses The pleura shows dense adhesions and pockets of fluid may be seen The ribs frequently become infected and sinuses develop as the process burrows through



FIG 7 *Actinomyces bovis* Sterile saline compress removed from draining abdominal sinus after 12 hours showing sulphur granules (arrows) caught in webs of gauze (Conant's technique)

the chest wall Such multiple sinuses are highly suggestive of actinomycotic infection

Abdominal actinomycosis — The intestinal tract becomes infected in about one fourth of the cases and since the first symptoms are those of inflammation in the ileocecal region and resemble acute or subacute appendicitis a history of an appendectomy is not uncommon A mass may develop in the right lower quadrant and one or more sinuses may form when the abdominal wall becomes involved When the colon becomes infected the picture closely resembles carcinoma The fungus bores relentlessly into adjacent structures and may involve the kidney liver and vertebral column causing cord compression or psoas abscesses Metastatic involvement of the brain is not uncommon The general symptoms are those of a severe subacute or chronic infection

Diagnosis — This depends in final analysis upon the demonstration of the ray fungus in the purulent discharges from sinuses The pathologist may be able to demonstrate the fungus in the appendix or other tissue removed at operation As a rule the characteristic sulphur granules are found with no great difficulty in the purulent discharges though occasionally repeated search may be required (Figs 5 and 6)

Dr Norman Conant has used the following method in the Duke Hospital Clinic for the demonstration of actinomyces in purulent discharges from sinuses Small pieces of the gauze dressings saturated with purulent discharge are examined under low power magnification The sulphur granules caught in the meshes of the gauze are seen readily (Fig 7) and then are transferred to a glass slide and examined under higher magnification Sputum should be spread thinly in a petri dish and searched for granules

The *prognosis* depends upon the area of the body infected It is always very serious in the abdominal form slightly less so in thoracic infections and best in cervicofacial and localized dermal infections At best actinomycosis is a stubborn chronic disease difficult of cure

MADURAMYCOSIS (MADURA FOOT)

When the foot is infected with actinomyces or other fungi a clinical picture is produced which cannot be distinguished from the brawny fistulous lesion of cervicofacial actinomycosis (Fig 8) The diagnosis is established by finding granules in the purulent discharges Such granules may be of various colors depending upon the fungus producing the infection The finding of spores in the granule indicates that the infection is caused by one of the molds differentiating it from infections caused by an actinomycete In general the treatment is that of actinomycosis and although the general health remains good amputation of the foot usually is necessary



Fig 8 Madura foot

Blastomycosis

Etiology — The disease is caused by the invasion of the body by *Blastomyces dermatitidis* which appears in the tissues as a round thick walled budding yeast like fungus and produces a chronic granulomatous type of inflammation It was described first by Gilchrist in 1896 and is known as North American blastomycosis to distinguish it from Cryptococcosis or European blastomycosis It may infect any part of the body but shows a predilection for the skin lungs and bone The source of the infection in nature is uncertain and it is only slightly contagious No age sex or race is exempt

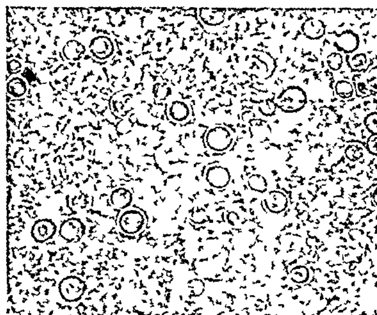


Fig 9 *Blastomyces dermatitidis* as seen in pus from a subcutaneous abscess The fungus appears as round double contoured budding yeast like cells Magnification [illegible]

Symptomatology — Two distinct clinical types are recognized superficial or cutaneous blastomycosis and generalized or systemic blastomycosis Curiously *the cutaneous form rarely produces deep or systemic lesions though the same* organism can cause both types of infection

The cutaneous form of blastomycosis begins as a papule or papulopustule of the skin particularly of the face hands wrists feet or ankles In the purulent discharge or from curettings of the lesions the fungus may be found (Fig 9) and



FIG 10 Blastomycosis The heaped up crusted advancing edge of the lesion with scar tissue formation in the center is quite characteristic

this represents the only certain means of diagnosis The infection spreads peripherally with scar tissue formation in the more central portions (Fig 10) The *advancing edges of the ulceration are heaped up and present a finely papilliform or verrucous appearance which is characteristic*

In the *systemic disseminated* form of blastomycosis the portal of entry usually is in the respiratory tract 95 per cent of such cases show pulmonary involvement at autopsy In one half the recorded cases of systemic blastomycosis the lungs were affected primarily (Fig 11) with secondary generalization In 59 autopsied cases the bones and joints were infected in 60 per cent the vertebrae being involved in 40 per cent of these (Fig 1) The central nervous system had been *invaded in 7 per cent of these cases psoas abscess was found in 3 instances* Blastomycosis of the lungs so closely simulates tuberculosis that neither physical examination nor roentgen ray studies can be relied upon to differentiate them In all instances of suspected tuberculosis where the tubercle bacillus cannot be demonstrated fungus infection should be suspected Carcinoma of the lung also may present a problem in differential diagnosis

In its beginning the disease presents the picture of a non specific respiratory *infection with dry hacking cough low grade fever and slight dyspnoea on exertion After weeks or months as the pulmonary infection progresses the fever dyspnoea* and weakness increase and the sputum becomes purulent and often bloody The pleura mediastinum and pericardium may be invaded and general dissemination of the fungus occurs throughout the body With the occurrence of systemic invasion symptoms of pyemia develop chills irregular fever night sweats and loss of strength and weight Symptoms referable to the sites of metastatic *infection now appear the bones liver spleen kidneys and central nervous system becoming involved in the frequency of their enumeration*

Diagnosis — The physical and x ray signs closely resemble massive tubercular infection or pulmonary abscess Occasionally enlargement of mediastinal lymph nodes is striking and in most cases irregular masses are seen projecting from the hilum of the lung When the sputum is bloody cancer is strongly suggested The only certain answer is to be found in sputum examinations

If blastomycosis is suspected and pus from the lesions examined in 10 per cent *potassium hydroxide and cultured the diagnosis is made easily* Exudates from all cutaneous abscesses and sinuses should be examined for fungi and if they are not found it is advisable to examine tissue obtained by gentle curettage Errors commonly are made in the diagnosis of the pulmonary form and many patients suffering from blastomycosis have been treated wrongly for tuberculosis With multiple abscesses and symptoms of septicemia generalized blastomycosis should be suspected

Prognosis — In systemic blastomycosis the prognosis is very bad Martin and Smith found a mortality of 9 per cent in patients who had been followed



Fig. 11.—Blastomycosis of the lungs.

for 2 years or more. *Cutaneous blastomycosis* offers a good prognosis as to life, rarely having a fatal outcome, but it is a stubborn, chronic disease, often persisting for years in spite of all treatment.

Treatment.—Because of observed bad reactions to iodide therapy in patients who are hypersensitive to the fungus, the following routine has been adopted in the Duke Hospital Clinic:



Fig 12 North American Blastomycosis The fungus has invaded the spine causing destruction of the bodies of the vertebrae and the formation of a paravertebral absces

A skin test should be done on every patient before any course of therapy is outlined The skin test is performed by the intracutaneous injection of 0 1 c c of a standardized heat killed *blastomyces* vaccine The site of injection should be observed at 24 and 48 hour intervals to determine the size of the maximal reaction

If the erythematous reaction is less than 1 cm in diameter, it is generally safe to administer potassium iodide by the rapid method outlined below A reaction 1 cm or more in diameter indicates hypersensitivity and the patient should be desensitized The desensitization procedure consists of the subcutaneous injection of gradually increasing amounts of vaccine, beginning with this material diluted in saline

The proper dilution of vaccine for the first desensitization injection can be estimated from the size of reaction observed in the skin test If the skin test material produced an erythematous zone about 2 cm in diameter the vaccine should be diluted 1 to 100 for the first injection A 1 to 1 000 dilution should be used if the skin reaction was as large as 5 cm in diameter, if the reaction is larger than this, it is unsafe to inject the vaccine unless diluted at least 1 to 10,000

The initial dose should be 0 1 c c of the indicated dilution injected subcutaneously and the dose increased by 0 1 c c every other day, or 3 times a week, until 1 0 c c is injected The procedure then is repeated beginning with 0 1 c c of the next lowest dilution until undiluted vaccine is administered It is important to keep the dose below that capable of producing severe local or general reactions In case reactions occur especially if the patient develops fever the vaccine should be discontinued for several days and then resumed but beginning with an injection one tenth as strong as that producing the reaction Some patients reach a limit in their tolerance to the vaccine making it impossible to increase the dose without reaction Complete desensitization is not to be expected and is not necessary Skin tests after vaccine administration usually show a marked reduction in the size of the erythematous reaction, and sterile abscess formation is abolished completely

Iodides can be started after about weeks of vaccine treatment but it is essential that this drug be administered cautiously and at a rate no faster than that outlined under the slow method of iodide therapy as already described under the general heading Treatment Vaccine injections should be given during the first few months of iodide treatment and may be continued for some time after apparent cure

SPOROTRICHOSIS

This is a chronic granulomatous inflammation of the skin lymph nodes or subcutaneous tissues caused by *Sporotrichum Schenckii* The disease is found widespread throughout the world and no age or race is exempt

Etiology — It is thought that man acquires sporotrichosis from contact with plants though in some instances the infection has been traced to infected animals who serve as carriers Horses dogs cats and rabbits may have spontaneous sporotrichosis Of 109 instances of human infection reported by Foerster 90



FIG 13 Sporotrichosis showing the ulcerated initial lesion and typical lymphatic spread

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The initial dose should be 0.1 c.c. of the indicated dilution injected subcutaneously and the dose increased by 0.1 c.c. every other day, or 3 times a week, until 1.0 c.c. is injected. The procedure then is repeated beginning with 0.1 c.c. of the next lowest dilution until undiluted vaccine is administered. It is important to keep the dose below that capable of producing severe local or general reactions. In case reactions occur especially if the patient develops fever the vaccine should be discontinued for several days and then resumed but beginning with an injection one tenth as strong as that producing the reaction. Some patients reach a limit in their tolerance to the vaccine making it impossible to increase the dose without reaction. Complete desensitization is not to be expected and is not necessary. Skin tests after vaccine administration usually show a marked reduction in the size of the erythematous reaction, and sterile abscess formation is abolished completely.

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and these secondary nodules may become necrotic producing secondary ulcers. The process may not reach the lymph nodes of the axilla or groin but if it does these may or may not break down forming suppurating ulcerations. The primary lesion may have healed before the patient is seen and the secondary lesions may persist for months or years if untreated. The patient is afebrile and remarkably free from symptoms.

When the infection becomes disseminated, which occurs rarely, skin nodules and ulcers develop as just described and the patient is acutely ill, becomes cachectic and death may result within a period of weeks or months. When the bones or various viscera become infected the symptoms are those resulting from any chronic granuloma of the organs involved.

Diagnosis. — This can be made with certainty only by culturing of the sporotrichum from the suppurating discharges since it is practically impossible to demonstrate the fungus microscopically in discharges from ulcers or sinuses (Fig. 14). The characteristic clinical picture easily leads one to a tentative diagnosis but other granulomatous types of infection such as syphilis and tuberculosis occasionally may present a very similar picture.

The *prognosis* is excellent in localized lymphatic sporotrichosis, the infection yielding readily to treatment with potassium iodide but the disseminated form may be very resistant to all therapy and result fatally.

COCCIDIOIDOMYCOSIS

Etiology. — This highly infectious disease is caused by *Coccidioides immitis* and was believed until recent years to be almost confined to the San Joaquin Valley, in California, hence the names Valley Fever and Desert Rheumatism by which the primary infection was known formerly. It is now recognized to be widely spread over the South West and it is thought that the infection is acquired by inhalation of dust from soil contaminated with the fungus.

Symptoms. — The disease appears in two forms which are so dissimilar that for a long time they were not recognized as manifestations of the same underlying infection. These are (1) primary coccidioidomycosis and (2) progressive coccidioidomycosis or coccidioidal granuloma.

The primary type of coccidioidomycosis produces symptoms of a more or less severe upper respiratory infection and the original diagnosis usually is influenza, bronchitis, bronchial pneumonia or atypical pneumonia. In one or two weeks the respiratory symptoms subside usually with complete return to normal but 2 or 3 per cent. of patients develop allergic phenomena manifested by skin lesions over the extremities closely resembling those of erythema multiforme or erythema nodosum. An acute arthritis may occur.

Various x-ray changes may be noted but none is at all diagnostic. The x-ray

were of the localized lymphatic form and in 62 of these the primary lesion was on the fingers or hands

Symptomatology — The infection presents itself most often as a small ulcer or nodule of the hands or feet but it may become disseminated without the oc

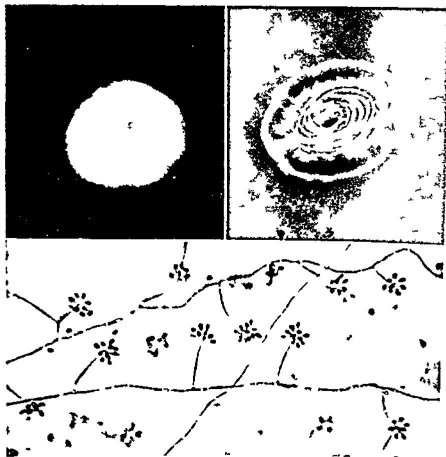


Fig 14 *Sporotrichum Schenckii* The upper figure shows non pigmented and pigmented colonies of the fungus growing on Sabouraud medium Below is a microscopic preparation of the fungus

currence of a detectable skin lesion In the rare cases of disseminated sporotrichosis ulcerative lesions may develop in the nose mouth or pharynx in the skin which may be extensively involved in the bones and in the viscera The lungs are infected only rarely in contrast to infections caused by other types of fungi

When the skin is infected a hard non tender nodule forms beneath the skin which later on involves the skin and breaking down forms a necrotic ulcer (Fig 13) The infection spreads upward along the course of lymphatic drainage

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Coccidioidomycosis

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Various x ray changes may be noted but none is at all diagnostic The x ray

plates may show hilar thickening a pneumonic infiltration or nodular lesions in the lung parenchyma which are more characteristic than the hilar adenopathy which is not rare

The fungus may invade the skin and lymph nodes, when the lungs are not involved primarily producing nodules which break down into ulcers or draining sinuses Rarely widespread dissemination occurs from skin and lymph node foci Primary coccidioidomycosis is a mild disease with practically no mortality,



FIG 15 *Coccidioides immitis* as seen in pus appearing as round thick walled spherules One is filled with endospores the other is collapsed Magnification 400

but an occasional patient will develop the chronic progressive coccidioidal granuloma which is among the most deadly of all known infections Fortunately only about 0.2 per cent of patients having the primary type develop the progressive form of the disease

It is difficult to foretell which patient showing primary coccidioidomycosis will develop the progressive type although coccidioidal granuloma is much more frequent in laborers of foreign extraction The patient destined to develop the malignant form usually shows evidence of the persistence of the fungus infection within a period of weeks or months after the primary infection In such patients physical and x ray signs of massive infiltration of the lungs develop rapidly with dyspnea cyanosis mucopurulent sputum sometimes bloody in which the characteristic fungus spherules may be detected The patient looks very ill and emaciates rapidly The fungus becomes disseminated widely in the body invading bone joints skin and various internal organs Death usually occurs within a few weeks or months

Diagnosis — This can be made positively by finding the fungus spherules in the purulent discharges gastric contents or subcutaneous abscesses (Fig 15) The injection of infected material into the testis of a guinea pig produces in about a week an abscess in the pus of which *C immitis* can be identified microscopically

Further discussion of coccidioidomycosis will be found in Chapt XIV-B of this volume

Moniliasis

Of the large group of yeast like organisms of the genus *Candida* only one *C albicans* has been shown to be an important pathogen for man As a rule it is a harmless saprophyte but under certain conditions it develops a mild pathogenicity It is found so frequently in normal individuals or accompanying infections with various organisms that often it is difficult to decide what role it plays in a disease process



Fig 16 Monilia infection of the toes and nails

The mucous membranes of the mouth not infrequently are infected with *C albicans* producing the mild inflammatory reaction known as thrush and the skin of the hands and feet (Fig 16) and membranes of the vagina are often the

plates may show hilar thickening, a pneumonic infiltration or nodular lesions in the lung parenchyma which are more characteristic than the hilar adenopathy which is not rare

The fungus may invade the skin and lymph nodes when the lungs are not involved primarily producing nodules which break down into ulcers or draining sinuses Rarely widespread dissemination occurs from skin and lymph node foci Primary coccidioidomycosis is a mild disease with practically no mortality,



FIG 15 *Coccidioides immitis* as seen in pus appearing as round thick walled spherules One is filled with endospores the other is collapsed Magnification 00

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Fig 18 Monilia albicans infection of lung showing diffuse fibrosis with nodular areas of infiltration

tion and the nails become hardened thickened and grooved These onychia and paronychia are prone to affect those whose hands or feet are constantly wet Similarly intertrigo due to C albicans is seen in moist areas of the body such as the axillae groin gluteal folds and under pendulant breasts Pruritis ani may



Fig. 17. *Monilia albicans*. Above, as seen in sputum and below, stained by Gram's method.

site of a mild but troublesome localization of the fungus. Obesity, diabetes and profuse sweating are predisposing factors.

Symptoms.—Several clinical types of *C. albicans* infection are seen. The region of the finger and toenails often is involved, producing a painful inflamma-

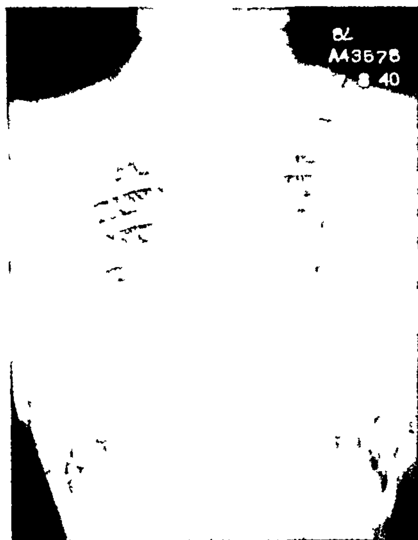


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be due to *C albicans* The infection may be so widespread as to be designated generalized and an allergic response consisting of groups of vesicles is seen, which corresponds to the ids seen in the dermaphytoses

Diagnosis The localized skin lesions often are irritating and resistant to therapy but none is fatal A more serious event is the infection of the bronchi and especially the lungs The bronchitis due to *C albicans* often is very chronic with progressions and relapses producing moderately profuse amounts of clear sputum containing flakes in which *C albicans* can be found (Fig 17) On x ray a finely linear fibrosis may be seen

Pulmonary moniliasis is an uncommon affection and is much more serious than the bronchial form The fungus produces a patchy pneumonia with fibrosis An experienced roentgenologist can differentiate the picture from tuberculosis but clinically this is rather difficult since the pneumonia closely resembles other types of bronchopneumonia (Fig 18)

Even the finding of *C albicans* in the sputum is not diagnostic unless it can be demonstrated with constancy and other infective agents excluded Direct examination cultural studies and animal inoculation all may be required

Prognosis — The localized types of oral vulvovaginal and cutaneous moniliasis usually respond readily to treatment but relapse is common especially when the predisposing factors are duplicated The chronic types of glossitis and vulvovaginitis may persist for years Patients with generalized cutaneous moniliasis or hypersensitive patients with monilids are extremely resistant to treatment and sometimes fail to respond after weeks of diligent therapy Patients with the bronchial and pulmonary forms of the disease usually recover although pulmonary moniliasis occasionally is fatal The prognosis is hopeless in patients with endocarditis or meningitis

CRYPTOCOCCOSIS (TORULOSIS)

This disease is better known to clinicians as *torulosis* but mycologist have shown it to be a blastomycosis caused by *Cryptococcus neoformans* formerly called *Torula histolytica* It is peculiar among fungus infections in that it shows a very strong predilection for the meninges and brain and cryptococcus (torula) meningitis is the lesion most familiar to internists However like all fungi it often infects the lungs and may spread to many other tissues of the body In reviewing 47 cases from the literature Levin found the nervous system involved in 30 the lungs in 9 and 8 patients had the generalized type of infection

Symptoms — The pulmonary form must be differentiated from tuberculosis which it resembles on physical examination and by x ray This can be done only by the demonstration of the fungus in the sputum When the central nervous system is involved the clinical picture is that of a slowly developing

meningitis and confirmation of this is found in the spinal fluid In spite of the seriousness of the meningitic infection the patient does not seem very ill the fever is not high the pulse seldom above 100 and the leucocytes and sedimentation rate are only slightly elevated As the disease progresses there is marked loss of weight and strength the patient ultimately becoming comatose and dying from respiratory failure

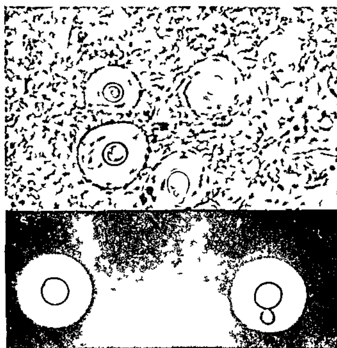


Fig 19 *Cryptococcus neoformans* The upper figure shows the round thick walled budding fungus in pus In the lower figure is shown an India ink preparation from the spinal fluid which demonstrates the budding fungus surrounded by its heavy capsule Magnification 850

Diagnosis — The clinical diagnosis can be made only by the demonstration of the fungus Errors in diagnosis can be avoided by suspecting cryptococcosis in all chronic meningitides The small organisms may be mistaken very easily for white or red cells and when searching for them in the spinal fluid the light should be reduced since their capsules are transparent and difficult to see By placing a drop of diluted India ink in the microscopic preparation the fungus is rendered more apparent (Fig 19) Pus from the skin lesions should be examined the same way

The *prognosis* is very bad when the central nervous system is infected the patients usually dying within 3 to 6 months although they may live for years The sulfonamides and penicillin recently have offered a faint ray of hope The lung skin and generalized lesions may heal spontaneously

ASPERGILLOSIS

Etiology — Certain species of the common fungus *Aspergillus*, show a mild pathogenicity for man The fungus may cause inflammatory reaction in the external ear in the skin nasal sinuses bronchi or lungs Pigeon breeders who often chew up grain before feeding it to the birds and wool sorters are especially prone to infection

Symptomatology — *It is always difficult to decide whether the fungus is a* primary or secondary invader When the fungus is found in quantity in any suppurating lesion or in the sputum it is a matter of clinical judgment as to how serious the contaminant is It is said to occur as a primary infection of the lungs producing the symptoms of pulmonary tuberculosis with very distressing cough The external auditory canal is affected most often and then is associated with a rather stubborn type of inflammatory reaction

Diagnosis depends upon the finding of the aspergillus in quantity and frequency sufficient to justify a belief in its primary pathogenicity The *prognosis* is good as to life but eradication of the fungus often is difficult With marked pulmonary fibrosis due to aspergillosis little can be expected from therapy

GEOTRICHOSIS

Certain species of *Geotrichum* may invade the body chiefly the mouth and lungs and the lesions produced must be differentiated from moniliasis and tuberculosis This can be done only by the repeated demonstration of the fungus in the superficial mucous membrane lesions or in the sputum

The bronchopulmonary form produces symptoms and signs so like tuberculosis that it cannot be diagnosed with certainty either by physical examination or x ray studies The finding of rectangular or oblong cells with square or rounded ends is diagnostic if these can be demonstrated in the discharge with constancy (Fig 20)

Diagnosis — The pulmonary form of the disease may be suspected from the presence of the mucoid glutinous sputum but only the finding of geotrichum confirms the diagnosis The lesions in the mouth resemble thrush or oral moniliasis from which it must be differentiated by microscopic and cultural studies



FIG 20 *Geotrichum* The fungus as seen in pus ... rectangular with rounded ends. Magnification 375

HISTOPLASMOSIS

In 1905 Darling at Ancon Hospital studied at autopsy a case characterized clinically by irregular fever emaciation anemia leukopenia and splenomegaly The essential pathological features were The invasion of endothelial cells in the small lymph and blood vessels and capillaries by enormous numbers of a small encapsulated microorganism causing necrosis of the liver with cirrhosis splenomegaly pseudo-granulomata of the lungs small and large intestines with ulceration of the latter and necrosis of lymph nodes draining the injected viscera The organism was named by Darling *Histoplasma capsulatum* and the disease is known as the histoplasmosis of Darling Edna Tompkins of Vanderbilt University was the first to recognize the disease during the life of the patient She found the yeast like parasites within large mononuclear cells in film of peripheral blood stained by supravital methods De Monbreun at the autopsy of this case obtained material from which *Histoplasma capsulatum* was cultivated successfully for the first time and shown to be the etiological agent of the disease by animal inoculation

Many instances of histoplasmosis have been described since Darling s publi

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cation but only rarely has the diagnosis been made before death The fungus is believed to enter the body either by the intestinal tract or from primary infection of the nose and throat Children are infected more often than adults but the disease shows the same fatal progress in both

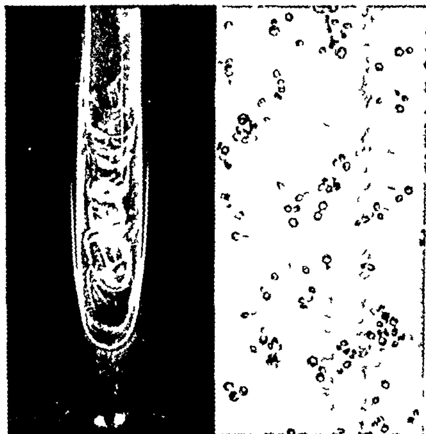


FIG 22 *Histoplasma capsulatum* The fungus is shown growing on a blood agar slant at the left and a microscopic preparation from the growth is shown on the right

Symptoms — The onset is insidious with a low grade fever diarrhea and loss of strength and weight The liver and spleen enlarge and there is a leukopenia Especially in adults there may develop marked adenopathy of the neck suggesting Hodgkin s disease or tuberculosis It is very common for the bone marrow to be the site of infection thus accounting for the anemia which is constant As in other fungus diseases the lungs mucous membranes and skin may be infected An instance of endocarditis has been reported



Fig 21 *Histoplasma capsulatum* Above a large mononuclear cell from the circulating blood is shown filled with the fungus Below macrophages of the liver contain numerous organisms

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Diagnosis — Histoplasmosis can be diagnosed during life by finding the characteristic organism in the large mononuclear cells of the circulating blood or bone marrow. Both thick and thin smears should be made and stained with either Wilson's, Wright's or Giemsa's stains (Fig 21). The fungus will grow in the peritoneal cavity of guinea pigs or mice and may be cultivated on Sabouraud's glucose agar or upon blood agar (Fig 22).

The disease is universally fatal, death ensuing within a few months. For further discussion of Histoplasmosis see Chapt XIV-A in this volume.

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CHAPTER XIV-A

HISTOPLASMOSIS

Reticuloendothelial Cytomycosis Histoplasmosis of Darling Cytomycosis of Darling

By HENRY PINKERTON

TABLE OF CONTENTS

Definition — A subacute or chronic systemic infection of high mortality affecting all age groups and caused by a fungus *Histoplasma capsulatum* The clinical picture is remarkably protean and may suggest primary disease of the hemopoietic system the gastrointestinal tract the lungs the nasopharynx the skin or the joints

HISTORICAL

In 1906 Darling[1] described a relatively large encapsulated organism in the tissues of a fatal case of a generalized infection occurring in the Panama Canal

appears to be the pathogenic phase measures about 3 x 3 5 micra in the active growth phase but forms two or three times as large appear in older cultures and have been described also in human tissues For maintenance of the rounded pathogenic form cultivation on blood agar or other protein rich media is believed to be necessary The organism is an obligate aerobe Its taxonomic status is somewhat uncertain De Monbreun found it not completely identical with *Cryptococcus farciminosis*

The presence of the organism in large numbers within the cells of infected tissues its cultivation on cell free media and the transmission of the infection to several experimental animals with reproduction of its characteristic pathological lesions leave no doubt concerning the etiological relationship of *Histoplasma capsulatum* to the human disease with which it is associated

Largely on the basis of variation in size of the organism it has been suggested that variations in species may occur and that localization in different organs may depend upon this factor Considerable variation in size may occur in different organs in the same case however and there is at present little evidence for assuming the occurrence of more than one species of the organism The organism is being cultivated with increasing frequency and detailed studies of a number of strains soon will be available Species and strain differences if they occur thus will be brought to light

Organisms of roughly similar size and shape which must be differentiated from *Histoplasma* in tissues are 1) *Leishmania* and *Trypanosoma cruzi* (aflagellate forms) 2) *Toxoplasma* 3) *Sarcocystis* and 4) *Encephalito oon cuniculi* *Leishmania* and *Trypanosoma cruzi* may be identified by the presence of a rod shaped kinetoplast in addition to the nucleus *Toxoplasma* *Sarcocystis* and *Encephalito oon* bear only a superficial resemblance to *Histoplasma* The refractile capsule which is a prominent feature of *Histoplasma* is lacking in the four organisms mentioned above

Epidemiology

Problems concerning the mode and route of infection to a large extent are unsolved De Monbreun[7] found *Histoplasma capsulatum* proven by cultural studies as the cause of a spontaneous infection in a dog Organisms identical with, or closely related to *Histoplasma capsulatum* have been found in ferrets and in mice

Experimentally the infection is transmissible to dogs by the oral route and by parenteral injection The fact that in several human cases lesions have been confined to the lungs suggests the respiratory tract as a possible route of infection Intratracheal injection of cultures in dogs and guinea pigs has however given

Zone The pathological lesions resembled those of tuberculosis In the same year Strong, while working in the Philippines, found a similar organism in curettings from an abscess of the chest, which healed following the application of antiseptic dressings

In 1908 and 1909 Darling reported two fatal cases similar to his first case Darling named the organism *Histoplasma capsulatum* Because of its general similarity in size and shape to the etiological agent of kala azar he believed it to be a protozoon but Rocha Lima in 191 expressed the opinion that it was a fungus closely related to *Cryptococcus farciminosis* the etiological agent of infectious lymphangitis of horses Final proof of the fungal nature of the organism was furnished in 1934 by De Monbreun[3] who first cultivated the organism on dextrose agar and Sabaraud s medium

Between 1908 and 1926 occurred a latent period during which no cases of histoplasmosis were recognized Two cases were reported in 1926 and two in 1932 In 1940 Meleney[4] was able to summarize 32 cases, the majority of which had occurred during the preceding fifteen months and recent reports indicate that the condition is being recognized with greatly increasing frequency

Incidence and Geographical Distribution

From available data it is not possible to say whether or not the rapidly increasing recognition of histoplasmosis represents a true increase in incidence It is, however clear that the disease can no longer be considered as excessively rare and that it must be considered seriously in the differential diagnosis of several clinical syndromes with which the physician frequently is confronted During the past three years 7 cases have been recognized in St Louis Missouri

Of 48 cases reported and unreported which have come to the attention of the author, 39 have occurred in the United States widely separated regions such as Florida Minnesota and California being represented The occurrence of the disease in the Canal Zone England Argentina Brazil the Philippines and Java suggests that the distribution may prove to be practically world wide

Etiology

The etiological agent is a fungus readily cultivated in a variety of media appearing in culture both as a rounded doubly contoured yeast like body reproducing by budding and in the form of mycelial threads The refractile capsule of the rounded form usually remains unstained in tissues while the central portion is most often basophilic The central part may stain uniformly but crescentic or signet ring configurations are quite characteristic The yeast like form, which

Pathology

A wide variety of gross pathological lesions are seen postmortem depending on which organs are involved most conspicuously. In the majority but not all, of the cases there has been found a generalized enlargement of the superficial and deep lymph nodes with splenomegaly. Localized opaque nodules varying from miliary size to 2 cm in diameter often are found in one or more organs and in general the gross picture has resembled that of tuberculosis. Caseation necrosis of the adrenals grossly like that of tuberculosis is a common finding and may be the only finding.

About a third of the cases have shown extensive ulcerative lesions situated in the ileum or large intestine or in both. The ulcers vary from pinpoint size to 2 cm in diameter, and usually they erode only the mucosa and submucosa. In one case however death resulted from perforation of an ulcer with resultant general peritonitis. In a number of cases lesions have been confined to the lungs and in another small group entirely to the skin or to the naso oral cavity. In several cases of the pulmonary type the lesions have been associated with those of tuberculosis.

Microscopically small focal lesions with central giant cells and surrounding macrophages resembling tubercles (Fig 1) are often but not invariably found. In accordance with the gross picture focal necrotic or proliferative lesions are found in many organs. The most conspicuous histological feature is the organism itself which is commonly present in huge numbers within cells in the lesions (Fig 2).

The regular arrangement of the intracellular organisms with surrounding clear rings often gives a honeycombed appearance to large areas of tissue. The organisms may, however be absent from the lesions in certain organs but present in large numbers in similar lesions in other organs from the same case. Organisms are most numerous at the edges of necrotic lesions and are often absent from the proliferative tubercle like lesions.

In general the cells in which the organisms are found are those of the reticuloendothelial system and the name reticuloendothelial cytomycosis has been applied aptly to the disease[3]. The fungus also invades epithelial cells however including those of the intestinal mucosa the liver and the adrenal. In the latter organ adrenal cortex cells have been found to be honeycombed with organisms over large areas with little inflammatory cell reaction.

The prostate has been involved in several cases and in at least two cases both organisms and lesions have been present in practically all organs and tissues of the body. In two cases friable vegetations have been present on the heart valves to cause a clinical picture like that of subacute bacterial endocarditis.

negative results On the whole the gastrointestinal and cutaneous routes seem to be the most probable portals of entry In several infantile cases there has been otitis media and fungi have been found in the discharge *from the ear suggesting* that the otitis media may have been the primary lesion from *which the organism spread to cause the general infection*

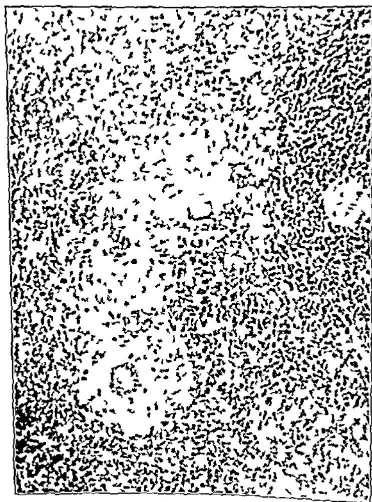


Fig 1 Histoplasmosis tubercle like lesions in spleen

The possibility of insect transmission from lower animals to man should be kept in mind also particularly in view of the fact that intracellular yeasts are known to occur in insects The organism is quite resistant, however and might live for a long time in soil

clinical picture been primarily that of ulcerative enteritis It is probable that regardless of the initial clinical picture the great majority of cases eventually die from generalized infection

Generalized Type

This type usually begins insidiously and the patient may have been in poor health for several weeks or months The actual illness is characterized by asthenia anorexia loss of weight and often by afternoon or evening rise in temperature Epigastric or lower abdominal pain may occur or generalized pain in the muscles joints or back There may be hoarseness and marked pharyngeal injection even though definite ulceration is not present The skin often is hot and moist Enlargement of the spleen and liver and generalized or localized enlargement of lymph nodes have been found in many cases The blood picture may be essentially normal but in many cases there has been severe anemia and leucopenia suggesting primary disease of the hemopoietic system

Cardiac Type

In a case reported recently the clinical picture was practically identical with that of subacute bacterial endocarditis Blood cultures were negative however and exploratory laparotomy was carried out because of the fact that the liver was palpable Biopsy of the liver showed tubercle like lesions in which histoplasma organisms were recognized This case terminated fatally fourteen days later Necropsy showed extensive vegetative endocarditis involving the mitral valve and a small warty lesion on the aortic valve Histoplasma organisms were present in large numbers in these vegetations There was evidence of healed rheumatic fever in the heart in this case and a single infarct was found in the spleen

An essentially similar case [1] recently was recognized in the Department of Pathology at the Washington University School of Medicine in reviewing the microscopic slides of a case in which necropsy was in 1928

In both of these cases tubercle like lesions were found in the viscera, and these were probably cases of the generalized type in which the organisms localized on the heart valves producing friable vegetations

Pulmonary Type

In several cases the clinical picture has suggested primary disease of the lungs and necropsy has shown the lesions confined to the lungs In two such cases[8]

Clinical Picture

On the bi is of present information it seems justifiable to describe several dif ferent clinical types of the di ease The clinical differences apparently depend



Fig 2 Histopla mo is ti ue from edge of a necrotic le ion in adrenal howing many intracellular organi ms note the clear zone around each organi m and the crescent or ignet ring appearance of the central bodie of the organi ms

to some extent on fortuitous localization of the infection Intestinal ulcers for example have been found po tmortem in 8 cases but in only 3 ca es has the

the cases with naso-oral ulceration eventually die of generalized infection even though the local lesion may be successfully treated

Cutaneous Type

This type may occur in conjunction with the naso-oral type and like the latter probably evolves finally into the generalized type The cutaneous lesions begin as papules which later become abscesses of variable size with indurated walls similar to lesions produced in other mycoses

Joint Involvement

Key and Large[1] have reported recently an interesting case in which marked inflammation and destruction of the knee joint was the presenting clinical feature The picture resembled tuberculosis of the knee joint but was believed later to be a low grade pyogenic infection in view of the fact that guinea pig inoculation gave negative results Amputation was done and the diagnosis of histoplasmosis was made by finding the characteristic organisms in the synovial membrane and adjacent bone tissue X ray examination of the chest showed extensive lung involvement probably by histoplasmosis This case terminated fatally after the operation and autopsy permission was not obtained

Infantile Cases

About one fourth of the reported cases have occurred in infants Nearly all of these have been of the generalized type with enlargement of the liver and spleen and anemia and leucopenia The onset is insidious with fever and failure to gain weight Diarrhea vomiting and evidence of upper respiratory infection with or without otitis media also are common early symptoms X ray evidence of pulmonary involvement has been present almost constantly in the later stages

Diagnosis and Differential Diagnosis

The generalized form of the disease may simulate kala azar miliary tuberculosis or other infectious diseases in which splenomegaly and prolonged irregular fever are prominent symptoms Cases with leucopenia anemia and lymph node enlargement must be differentiated from aplastic anemia aleukemic leukemia and lymphosarcoma Localized enlargement of lymph nodes may suggest Hodgkin s disease The intestinal type of the disease must be distinguished from amebic and bacillary dysentery ulcerative colitis tuberculous enteritis and re

there was an associated tuberculous infection, and in view of the general similarity of tuberculosis and histoplasmosis from the pathological point of view, it has been difficult to separate the two types of lesions from one another In certain lesions both tubercle bacilli and *Histoplasma* have been present side by side

The clinical picture of pulmonary histoplasmosis likewise is similar to that of tuberculosis Irregular fever, emaciation, cough night sweats and chest pain have been present in various combinations The x ray picture of pure pulmonary histoplasmosis probably is similar to that of tuberculosis This statement is based on the fact that in cases not complicated by tuberculosis x ray reports of ' irregular mottling suggesting minimal tuberculosis or hilar tuberculosis complicated by bronchitis and early bronchopneumonia have been returned The findings in one of Meleney s cases suggest that cavitation may occur in histoplasmosis uncomplicated by tuberculosis Extensive necrotic exudate has been found in the pleura in two cases

The absence of lesions from the other organs in these cases of pulmonary histoplasmosis suggest that infection may take place by way of the respiratory tract Tuberculous cavities may be the portal of entry as has been suggested in cases of torula infection

Intestinal Type

In at least 3 cases intestinal symptoms have dominated the clinical picture[3], and in several other cases such symptoms have been a prominent feature In all of these cases, however, postmortem studies have revealed the generalized type of infection and the only reason for considering these cases separately is the fact that they must be differentiated from other types of ulcerative enteritis In these cases frequent whitish, liquid stools without gross blood have occurred together with distention and slight tenderness of the abdomen Vomiting has been present in several cases Emaciation, anorexia fever and asthenia apparently are constant One case was mistaken clinically for amebic dysentery and macrophages laden with the rounded organisms *Histoplasma* apparently were mistaken for amebæ on microscopic examination of the stools

Naso oral Type

In cases of this type ulcerative lesions, either localized or confluent and single or multiple are found in the naso oral cavity These ulcers have raised indurated edges, and in one instance the picture led to a clinical diagnosis of epidermoid carcinoma of the tongue[5] This patient was in apparently good general health when first seen and the tongue lesion cleared up following radium implantation but death occurred months later, and necropsy was not done It is probable that

subsequent history has been followed for a long enough period to rule out the possibility of eventual fatal termination Since most cases have been diagnosed only at autopsy it is possible that milder cases with recovery may be recognized in the future

Treatment

At present treatment is largely symptomatic Sulfanilamide therapy has been ineffective in 3 cases Potassium iodide and neoarsphenamine have been tried without success Mantell and Troy[11] using neostam a pentavalent organic antimony compound obtained apparent success but Brown and his co workers [4] were unsuccessful with antimony and potassium tartrate In a case referred to above[5] an indurated ulcer on the tongue healed well following radium implantation but the patient died a few months later presumably of generalized infection Williams and Cromartie[1] report poor results and an early fatal termination following the use of radiotherapy in a case involving the naso-oral cavity

The transmission of the disease to monkeys dogs guinea pigs rats and mice makes it possible to test the value of therapeutic agents under controlled laboratory conditions For studies of this type the dog and rat appear to be most useful since generalized infection has occurred only in these animals

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gional ileitis Essentially pulmonary cases simulate chronic pulmonary tuberculosis Ulcers in the mouth or on the tongue in the early stages of the disease may be mistaken for carcinoma The cutaneous lesions suggest blastomycosis and other types of chronic cutaneous suppuration The case reported by Key and Large[10] simulated tuberculosis of the knee joint

From all of these conditions histoplasmosis is differentiated by culturing the specific etiological agent or by its demonstration in smears or sections of tissue Approximately 8 cases have been diagnosed during life by one or another of these methods The organisms when present within cells in large numbers, are so characteristic in appearance that a reasonably accurate diagnosis may be made in smears and sections on purely morphological criteria Organisms which bear some resemblance to *Histoplasma* have been discussed earlier in this chapter

The organism may be demonstrated in either thick or thin films of peripheral blood It is seen in monocytes in large numbers and occasionally in smaller numbers in neutrophiles The common methods of staining blood films are adequate, and the organisms appear as doubly contoured yeast like bodies This method is valuable only in late cases with systemic involvement Puncture of the bone marrow may offer a better chance of making a diagnosis and splenic puncture may be resorted to if simpler methods fail

Cultures of the blood and other materials should be made on Sabaraud's agar and dextrose blood agar and observed for several weeks as the organism may grow slowly in initial cultures Smith and co workers[1], however, obtained growth on blood agar plates incubated aerobically at room temperature on the third or fourth day following inoculation with blood taken from the heart at autopsy Animal inoculation, particularly in dogs rabbits guinea pigs and young mice also may establish the diagnosis Biopsy has led to a diagnosis in at least 4 cases An enlarged superficial lymph node may be removed easily for study In cases with pulmonary involvement since the alveolar macrophages often are laden with organisms, it is likely that a diagnosis could be made by sputum examination Recovery of the organism from stools and urine is possible

A specific cutaneous test for infection using supernatant fluid from broth cultures of the fungus has been described by Van Pernis Benson and Holinger[1] If this test proves to be reliable it should be of great assistance in establishing early diagnosis and in furthering our knowledge of the disease particularly with regard to the possibility of latent or inapparent infection

Prognosis

The disease appears to be practically always fatal Three cases with cutaneous or naso oral lesions have been cured clinically but it is doubtful whether the

CHAPTER XIV-B

COCCIDIOIDOMYCOSIS

By CHARLES EDWARD SMITH

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Definition.—Coccidioidomycosis is an infection caused by the fungus *Coccidioides immitis* Rixford and Gilchrist 1896. The initial or primary type of *coccidioidomycosis is usually a selflimited pulmonary infection.* It may be devoid of symptoms, may be characterized by a prostrating influenza-like illness *frequently accompanied by severe pleural pain or may have an associated* erythema nodosum or erythema multiforme. When such skin lesions have occurred the illness has been known as San Joaquin fever, valley fever, desert fever or desert rheumatism. *Because of the difficulty of pronouncing coccidioidomycosis* these names have been applied also to any initial coccidioidal infection even though erythema nodosum has not occurred and despite the fact that the infec-

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Etiology

Coccidioides immitis occurs in two characteristic forms On solid media it has a white cottony appearance (Fig 1) As cultures age they frequently become *slightly pigmented* The hyphae are septate and in older cultures chlamyd-

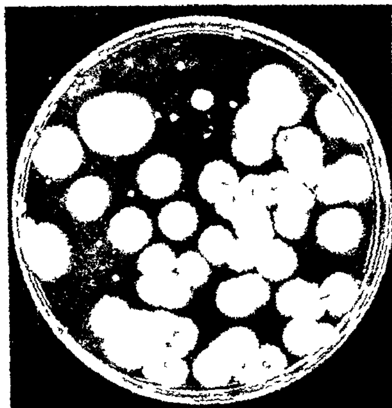


Fig 1 Sputum culture of *Coccidioides immitis* in Sabouraud's medium

ospores are abundant (Fig 2) The chlamydospores may be square rectangular or ellipsoidal from 2 to 10 micra in length and 2 to 5 micra in diameter Presumably this saprophytic phase is the one occurring in nature Rarely one sees sporangia the culture spherules of Baker and Mrak[3] Injected into or inhaled by animals similar sporangia always form These spherules constitute the so called parasitic phase of *Coccidioides* The hyphal spores become rounded and have doubly refractile walls The protoplasm is divided by cleavage planes and endospores are formed (Fig 3) Endospores may be arranged radially

tion may be required outside the San Joaquin Valley of California Also included under coccidioidomycosis is the disseminated, secondary or progressive infection known as coccidioidal granuloma the San Joaquin Valley disease or even as the California disease Special caution is necessary to avoid confusing coccidioido mycosis with coccidiosis

HISTORICAL

The first reported case of what we now recognize as disseminated coccidioido mycosis was described by Posada and by Wernicke[1] in 1892 It originated in Argentina After Rixford in 1894 reported a similar case, the first from North America he and Gilchrist studied the disease in detail With the advice of Stiles they decided that they were dealing with a sporozoon Because of its resemblance to the coccidia they named it *Coccidioides* In 1900 Ophuls and Moffitt reported that *Coccidioides* was a fungus and not an animal parasite During the next thirty six years it was studied by Ophuls[11] Wolbach[4] MacNeal and Taylor[1] Moore Dickson[1] Chope and other investigators in this country Among th most important foreign workers have been de Almeida in Brazil and Ciferri and Redaelli[10] in Italy

Many investigators have proposed other names for the fungus but all have been inappropriate or invalid with the result that now *Coccidioides immitis* Rix ford and Gilchrist 1896 is the accepted designation[1] The only recognized form of the infection coccidioidal granuloma was described in its multitudinous mani festations by scores of physicians almost every case being the motive of an article

The skin testing material coccidioidin was used by Davis[1] , Hirsch and Ben son[6] D Andrea[7], Jacobson[7] Stewart[48] Beck[6], Kessel[1] and others Giltner[3], Beck and Traum[6] Stiles and Davis[49] reported spontaneous localized, coccidioidal infections in cattle and sheep Beck summarized the information available on coccidioidal granuloma in 1931 In 1934 Stewart and Meyer[47] isolated *Coccidio ides* from the soil of a San Joaquin Valley ranch

What Meyer has termed the renaissance of *Coccidioides*[11] began in 1936 In that year Gifford announced that San Joaquin Valley Fever was caused by *Coccidioides* The discovery did not attract attention until the following year when Dickson[14] independently reporting the like d scovery, drove the message home in a series of very important articles the most outstanding of which was his joint article with Gifford[15] In these papers Dickson proposed the designation, coccidioidomycosis to include all forms of coccidioidal infection During the years since then a number of individuals have contributed to the tremendous in crease in our knowledge of this infection

germ tubes push out from the *endospores* or spherules to produce the hyphal saprophytic phase

Either the mycelial saprophytic phase or the sporangial parasitic form can be maintained indefinitely without altering the characteristics of the organism

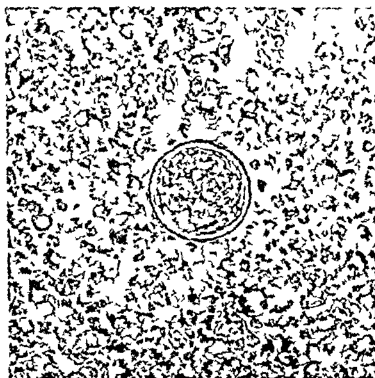


Fig 3 Mature sporangium (spherule) of *Coccidioides immitis* seen in pus

Production of endosporulating spherules in vitro by Lack and the discovery of culture spherules on solid media by Baker and Mrak[3] suggest that the parasitic phase is really the response of the organism to the relatively unfavorable animal environment in which it has assumed a form optimal for reproductive purposes

The taxonomic position of *Coccidioides* still is unsettled The septate character of its mycelium suggests that it is an Ascomycete but the sporangial nature of the spherule would relate it more definitely to the Phycomycetes Certain it is that the alteration from the mycelial to the spherule form is requisite for identification of the fungus as will be emphasized under the heading Laboratory Diagnosis

around the periphery of the spherules, may be few in number, or scores may pack the spherule When the spherule is mature the endospores are liberated by rupture of the spherule wall (Fig 4) The endospores develop into mature spherules to repeat the endospore spherule cycle within the animal host Usually mo e



Fig 2 Hyphae of *Coccidioides immitis* with free chlamydo pores from Sabouraud s culture one year old

frequent than spherules with endospores are spherules which are empty or contain undivided protoplasm The spherule wall sometimes is covered with spines and occasionally with clubs The sizes of the spherules commonly range from 10 to 60 micra although Schenken and Palik[3] observed giant spherules one of which was 262 micra in diameter The endospores are usually 2 to 5 micra in diameter When the infected animal dies or the spherules are outside the animal body

logical [1] evidence strongly support the theory that the infection is acquired by inhalation of chlamydospores blown about in the dust The fungus has been recovered from the soil by three groups of investigators [?] With spores present in the soil one would expect rodents to be infected even as cattle sheep dogs and man are *Certainly distribution of the fungus is restricted but the reason why cannot be given until we know its source in nature*

PATHOGENESIS

Practically all investigators concur with Ophuls that the usual portal of entry is the respiratory tract Occasional instances have been reported of entry through abrasions but most skin lesions are multiple the result of blood borne dissemination Coccidioidomycosis is not acquired by ingestion as the fungus appears to succumb to digestive secretions

The chlamydospores develop into spherules sporangia in the lungs producing a pulmonary infection No human material has ever been available for the study of the process but by analogy one would surmise that the process often is comparable to the initial tuberculous process The roentgenographic appearance may be strikingly similar The hilar glands may be greatly enlarged At times pneumonitis is extensive (Fig 5A) Frequently however there is nothing demonstrable roentgenologically This variability in evidence of involvement is matched by the variation in the clinical manifestations of primary coccidioidomycosis In from two days to three weeks after symptoms develop ten days to six weeks after exposure *sensitivity to the filterable products of Coccidioides* coccidioidin develops This sensitivity increases in degree at first the patient *will be sensitive only to a 1 100 dilution of coccidioidin while a week later he* may react vigorously to 1 10 000 coccidioidin Shortly after sensitivity is established often the patient will develop humoral evidence of infection demonstrable by precipitin and complement fixation tests

In the usual patient the infection is successfully focalized (Fig 5B) As in tuberculous infection the individual is left with a circumscribed lesion consisting mainly of scar tissue often with calcium deposits Also as in tuberculous infection the sensitivity to the appropriate skin testing antigen remains as demonstrable evidence of infection By contrast the humoral antibodies are relatively transient

Not uncommonly a small amount of pleural fluid may form during the primary infection In rare instances the effusion may be very extensive (Fig 6)

Occasionally a cavity or very rarely multiple cavities may develop in the lung parenchyma[10] (Fig 7) On a few occasions these cavities have been watched roentgenographically as they develop Often there is little inflammatory

No consistent cultural or morphological strain differences have ever been established. While strains may vary in pathogenicity to laboratory animals, there is no correlation with the type of human infections from which they were isolated. No strain differences have ever been noted in skin testing antigens[4], not even in strains isolated directly from soil without passage through man or laboratory animals. The reaction evoked by an autogenous coccidioidin does not differ from the response to any other coccidioidin.

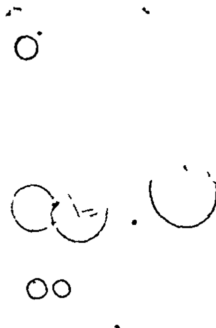


FIG 4 Sporangium spherule of parasitic phase with wall ruptured releasing the endospores

The growth requirements of the organism are very simple. It flourishes on a wide variety of media. Stewart and Meyer[43] recovered it in viable form from cactus on which the fungus had been planted seven years previously. It survives for years in soil and will withstand a wide range of temperatures. While it is not killed at −73° C it cannot withstand associated lyophile dehydration.

Where the organism multiplies in nature is unknown. Emmons[14, 15] suggests that wild rodents constitute an animal reservoir. Clinical and epidemio

similar to those of other infections and of many drugs The lesions appear when the peak of allergy has just developed [1] Sometimes they undergo an exacerbation or recurrence when the coccidioidin test is performed with too concentrated material [4] Frequently the coccidioidin reaction presents an appearance iden



Fig 5B Roentgenogram of patient with initial primary coccidioidomycosis Marked regression three months later

tical with the prevailing type of skin lesion Probably only 2 to 5 per cent of the coccidioidal infections are accompanied by these lesions The prognosis for such patients seems especially favorable

Classical coccidioidal granuloma occurs as a dissemination of pulmonary infection Fortunately it is very rare probably occurring in not more than 0 1 or 0 2 per cent of all infections Instead of being focalized in the lung the spherules are carried by the blood or lymph to other parts of the body where they continue

reaction around the wall of the cavity The most characteristic appearance is that of a thin walled cyst Evidence is strong that these individuals, like those without the mechanical defect have a well focalized infection, though exacerbations of reaction around the cavity walls do occur However, the focus does not



Fig 5A Roentgenogram of patient with initial primary coccidioidomycosis At height of illness

serve as a site for extension to other parts of the lungs or elsewhere in the body, even though the fungus persists in the sputum

Primary coccidioidomycosis frequently is complicated by erythema nodosum (Fig 8) or erythema multiforme true San Joaquin fever or valley fever[14 15 0 1] Evidence is conclusive that these skin manifestations are sensitivity phenomena

occasional infants very young children or aborigines whose initial tuberculous infections progress unchecked Then there is no interval between the initial infection and classical coccid~ ~ial granuloma the former merging imperceptibly into the latter



Fig 7 Solitary coccidioidal cavity

Experimental studies and epidemiological evidence indicate that one infection to *Coccidioides* confers a relatively solid immunity Previously infected and recovered animals can withstand massive doses of *Coccidioides* either in the form of chlamydospores or of spherules Microscopic lesions are demonstrable in these

to multiply These sites include meninges skin, bones or joints, subcutaneous tissue lymph nodes in fact any or all organs The dissemination usually is within a few months or even weeks after the infection is acquired Rarely cases are presumed to have developed years later Every effort should be made to



Fig 6 Extensive left pleural effusion associated with initial coccidioidomycosis

insure a thorough walling off of the primary infection when it occurs[41] Once this is accomplished the risk of dissemination never great drops to negligible proportions If an analogy with tuberculosis is drawn disseminated coccidioidomycosis must be considered as endogenous reinfection The victims are like

Pathology

The pathology of the acute primary infection of man has never been described because the infection is never fatal in this stage. Nor has it as yet been possible

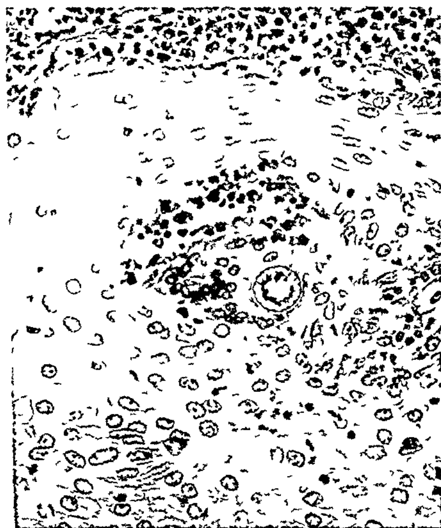


Fig 9 Microphotograph of disseminated coccidioidomycosis involving the skin showing typical granuloma with spherule of *Coccidioides* in giant cell

to examine the tissues of such a patient who has been the victim of accidental

animals but they do not progress to a size grossly visible Control animals subjected to much smaller doses develop progressive lesions to which they succumb

Practically all residents of the most important endemic areas have been infected Infection of laboratory workers is the rule rather than the exception However exogenous reinfections have never been proven in these groups, even though new arrivals to the same environments undergo infections

We have proven instances of the specific exposure of previously infected individuals who subsequently gave neither clinical nor laboratory evidence of new infections Persons never previously infected but subjected to these same exposures developed severe clinical coccidioidomycosis, proven serologically and by recovery of the fungus



FIG 8 Erythema nodosum occurring in initial coccidioidomycosis

Thus coccidioidomycosis is seen to conform to the well nigh universal biological pattern The infection is exceedingly common in its endemic areas with completely inapparent infections in the vast majority Clinically typical prostrating illnesses are common but the devastating disseminations, coccidioidal granuloma, are the great exceptions

regions are involved as it lies between the proven endemic regions of Arizona and Texas. Western and southern Texas[34, 61] have *Coccidioides* in considerable amounts. These are the only authentic endemic areas in the United States. Other semi arid regions in western states may well prove to be infected.

Instances of coccidioidal infection have been reported east of the Mississippi but diagnostic errors and failure to eliminate direct or indirect contact with the expanded, recognized endemic area probably explain these sporadic cases. In the rest of North America the northern arid states of Mexico most certainly are infected.

The Chaco region of Argentina is the only proven endemic area outside of North America. This is the site of Posada and Wernicke's original case and the only other cases of South America. It is to be recalled that the report of Brazil as an endemic area grew out of the confusion of *Paracoccidioides brasiliensis* with *Coccidioides immitis*.

Apparently authentic coccidioidal granuloma has been reported from Italy, the Balkans and the Hawaiian Islands. Failure to demonstrate more than a rare case strongly implies that coccidioidomycosis is not endemic and that these cases may have resulted from imported fungus. However the possibility exists that in some arid regions similar to our Southwest the fungus exists but as yet the infections are not recognized.

The proven endemic areas in North and South America have in common a semi arid to arid climate. Investigations in intensely desert regions of California like the Mojave Desert continuous to the San Joaquin Valley itself fail to reveal an appreciable incidence of clinical coccidioidomycosis or of coccidioidin reactors. These findings suggests that the climate there may be too dry. Geographical distribution may provide the lead for the discovery of the source of the fungus in nature. When we learn this source we shall certainly be in a position to delimit the distribution with much greater accuracy.

The incubation period of initial coccidioidal infection has been ascertained to lie between one and four weeks[41] generally ten to sixteen days. Knowledge of the incubation period is of material assistance in fixing sites of infection and thus demarcating endemic areas possibility of contagion and other epidemiological considerations.

One fundamental aspect of coccidioidomycosis is that of possible communicability. As has already been mentioned the usual portal of entry is the respiratory tract. The light minute chlamydospores are readily adapted to wide spread dissemination. Human infections have resulted from exposure to contaminated clothing and such dusty products as cotton and grain. However the spherules of the so called parasitic phase are not contagious. Persons live in the same home and even sleep in the same bed with patients undergoing severe

death or intercurrent fatal illness Biopsies of coccidioidal erythema nodosum lesions have revealed neither spherules nor differentiating tissue reaction

At autopsy the lungs of a person who has undergone an infection in the more remote past usually reveal a circumscribed fibrotic, frequently calcified lesion grossly indistinguishable from tuberculosis[11] The location of this lesion in a bronchial gland or subpleurally in the lung parenchyma gives additional striking analogy with primary tuberculosis Histologically there are the same epithelioid and giant cells The sole difference lies in the demonstration of coccidioidal spherules The fact that these lesions are typical granulomata provides a very valid objection to terming the progressive disseminated infection coccidioidal granuloma

The pathology of the disseminated infection has been described by Rixford and Gilchrist by Ophuls [4] and many others The lesions grossly and microscopically, again except for the demonstration of the causative organisms, are usually indistinguishable from tuberculosis (Fig 9) In some instances there tends to be considerable polymorphonuclear reaction This is especially true of clinical cases with multiple subcutaneous abscesses

Epidemiology

Knowledge of the distribution of *Coccidioides* still is incomplete The evidence which has been presented has consisted of the distribution of human coccidioidin reactors[4] or clinically recognized cases[4,39] of infections in cattle[4,13] sheep and dogs and of Emmon s recent recoveries of *Coccidioides* from the lungs of trapped rodents[17] Unfortunately many of the reported human cases are not authentic[4,3] the diagnosis being clearly erroneous or highly suspicious Moreover as the fungus can be carried on dusty products and even clothing a single clinical case or an isolated reaction to coccidioidin does not establish the endemicity of an area On the basis of the evidence at hand however the fungus is known to exist far beyond the San Joaquin Valley to which it has given dubious distinction In California scattered infections are found in the northern portion of the San Joaquin Valley and very frequently in the southern portion especially along its western slopes *Coccidioides* also occurs on dry Pacific slopes of the Coast Range though less heavily and down through San Benito Monterey, San Luis Obispo[4] and Ventura counties Information regarding the Southern California area is less accurate but the fungus apparently is found sporadically in all of the southern counties from Los Angeles to the Mexican Border East of California the southern half of Arizona from Phoenix south[1,16,19] is as heavily infected as the San Joaquin Valley The southern portions of Nevada and Utah also are apparently infected[13] Of New Mexico less is known but certainly some

fornia death rate of Negroes has been twenty three times that of Caucasians while that of Filipinos has been one hundred and eighty times that of whites Housing and diet play no discernible role

While no explanation can be offered it is apparent that white females are most prone to have their infections in a relatively benign form while dark skinned males *are most apt to disseminate their infections Thus factors of individual* sexual and racial resistance are important in enabling the patient to handle his infection even though they are without apparent effect in his acquirement of infection

Symptomatology

Primary or Initial Coccidioidomycosis

It is now apparent that many if not most coccidioidal infections are completely asymptomatic Others are accompanied by relatively mild respiratory or systemic symptoms which are indistinguishable from those of common colds There are all gradations in symptomatology from these subclinical infections to very severe prostrating illnesses

These severe manifestations may consist of any or all of the following signs and symptoms (1) *Pain in the chest* This symptom is one of the most characteristic and suggestive It varies from a mere tightness or sense of oppression to sharp knife like stabs which all but cut off respiration It may be the first symptom but frequently develops after one or several days ( ) *Cough* Frequently absent the cough generally is irritating non productive and often exceedingly persistent (3) *Malaise* This symptom also varies from a mere tired feeling to completely prostrating illness (4) *Chills* Chills while not constant are frequent and often initiate the illness (5) *Fever* Chills when present are usually accompanied by high fever The temperature may climb to over 105 F The usual range is 99 to 101 F characteristically with an afternoon peak (6) *Headache* Headaches are common and may be exceedingly severe (7) *Anorexia* Anorexia usually is profound The return of appetite frequently is one of the first indications that the patient is recovering Weight losses of twenty to thirty pounds often occur but are generally made up rapidly (8) *Nightsweats* Nightsweats too are frequent and may persist for several weeks They are often so drenching as to require changing of bedding (9) *Backache* Backache distinct from malaise often is marked (10) *Pharyngitis* Frequently a diffuse pharyngitis occurs It is rarely severe (11) *Macular rash* Not infrequently one or two days after the onset a generalized fine macular rash appears over the entire trunk often including the extremities Rarely wheals resembling hives *may occur These skin lesions come before sensitivity to coccidioidin is well*

coccidioidomycosis without becoming infected[11] Normal guinea pigs have been kept for months in cages with coccidioidal guinea pigs having draining testicular lesions without becoming infected No instance of direct man to man, animal to animal or animal to man transmission has ever been established Theoretically pus or sputum might lodge in crevices, and sprouting mycelia provide infective chlamydopores However the extent of such multiplication would be very limited Proper disposal of sputum in pulmonary cases and of dressings in drain ing disseminated cases will eliminate even that remote hazard Elaborate isola tion would seem unnecessary

The infectivity of the chlamydospores is attested further by the seasonal dis tribution San Joaquin Valley studies[11] have demonstrated that the peak of incidence of primary coccidioidomycosis is in the dusty season, while the ebb is in the winter during the few months of rain

With respect to susceptibility skin testing surveys have revealed no predilec tion for age, sex or race In the endemic areas infections are well nigh universal In the southern San Joaquin Valley nearly four out of five long time resident have a positive skin test [1] Some Arizona Indian tribes have had better than 94 per cent reactors[1] Admittedly some of these infections may have been due to *Haplosporangium par um* see discussion of coccidioidin under Laboratory Diag nosis

While age per se has no apparent effect on susceptibility to infection the longer the residence in an endemic area, the greater the proportion of infections In Kern County Gifford and her associates [1] found the percentage of coccidioidin reacting school children rose from 17 per cent for those resident less than one year to 77 per cent for those resident ten years and over Aronson s Arizona Indians[1] had few positive reactions under the age of two, but coincident with the close association of the toddler with the soil the incidence leaped almost to adult figures

While no sex difference has been demonstrated in coccidioidin surveys it has been observed that the male coccidioidal granuloma incidence has exceeded the female by from four to seven to one This was believed to be due to occupa tional exposure However coccidioidal erythema nodosum like tuberculous ery thema nodosum is much more common in females[41] The incidence of true San Joaquin fever is at least twice as great in females as in males

Similarly, while no racial difference is apparent in infection as revealed in coccidioidin surveys erythema nodosum is rare in Negroes and Filipinos[41] In these two groups progressive disseminated coccidioidal infection is especially com mon Various authors have commented on this susceptibility of the dark skinned races

In Kern County, California Gifford has shown that the coccidioidal granu

loma death rate of Negroes has been twenty three times that of Caucasians while that of Filipinos has been one hundred and eighty times that of whites Housing and diet play no discernible role

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Primary or Initial Coccidioidomycosis

It is now apparent that many if not most coccidioidal infections are completely asymptomatic Others are accompanied by relatively mild respiratory or systemic symptoms which are indistinguishable from those of common colds There are all gradations in symptomatology from these subclinical infections to very severe prostrating illnesses

These severe manifestations may consist of any or all of the following signs and symptoms (1) *Pain in the chest* This symptom is one of the most characteristic and suggestive It varies from a mere tightness or sense of oppression to sharp knife like stabs which all but cut off respiration It may be the first symptom but frequently develops after one or several days ( ) *Cough* Frequently absent the cough generally is irritating non productive and often exceedingly persistent (3) *Malaise* This symptom also varies from a mere tired feeling to completely prostrating illness (4) *Chills* Chills while not constant are frequent and often initiate the illness (5) *Fever* Chills when present are usually accompanied by high fever The temperature may climb to over 105 F The usual range is 99 to 101 F characteristically with an afternoon peak (6) *Headache* Headaches are common and may be exceedingly severe (7) *Anorexia* Anorexia usually is profound The return of appetite frequently is one of the first indications that the patient is recovering Weight losses of twenty to thirty pounds often occur but are generally made up rapidly (8) *Nightsweats* Nightsweats too are frequent and may persist for several weeks They are often so drenching as to require changing of bedding (9) *Backache* Backache distinct from malaise often is marked (10) *Pharyngitis* Frequently a diffuse pharyngitis occurs It is rarely severe (11) *Macular rash* Not infrequently one or two days after the onset a generalized fine macular rash appears over the entire trunk often including the extremities Rarely wheals resembling hives may occur These skin lesions come before sensitivity to coccidioidin is well

established and should not be confused with erythema nodosum or erythema multiforme

The acute illness may have an insidious onset or be sudden and prostrating Physical signs other than the fever are infrequent Sometimes there is a diffuse reddening of the throat and an accompanying cervical lymphadenopathy The rash has been mentioned also Examination of the chest will reveal rarely a friction rub signs of consolidation or a few rales Of course, if appreciable pleural effusion develops its signs are demonstrable

In association with hypersensitivity perhaps one patient in twenty to fifty will develop typical symmetrical erythema nodosum or erythema multiforme (Fig 8) These allergic manifestations may develop without any preceding respiratory phase but often occur when the initial illness is subsiding The erythema nodosum occurs in classical distribution over the anterior tibial surfaces, scattered or confluent especially around the knees and frequently extending up the lower third of the thighs and sometimes on the lateral surfaces of the thighs and buttocks Less frequently lesions of erythema nodosum also appear on the upper extremities and face

However erythema multiforme is more common than erythema nodosum on the upper extremities It develops most often on the margins of the palms of the hands, the lateral aspects of the arms and forearms in a collar distribution around the neck and occasionally on the face neck and upper thorax Usually erythema nodosum is present on the lower extremities when erythema multiforme occurs on the arms and neck but sometimes the latter occurs alone The skin lesions may all appear in the space of a few days but often come in crops during several weeks Frequently a new eruption will occur after exertion As they wane the lesions leave pigmented areas which may be discernible for months

Often there is severe arthritis coincident with the erythematous skin lesions This manifestation has given rise to the name, desert rheumatism Any joints may suffer ankles knees, hips wrists elbows shoulders or fingers There is rarely any swelling or redness and hydrarthrosis has not been observed The arthritis may persist for weeks and be very incapacitating Phlyctenular conjunctivitis also is common in this allergic phase Edema of the ankles sometimes develops but is explainable on the basis of the mechanical interference with lymph flow by erythema nodosum lesions In one such patient in whom an Addis concentration test could be performed, there was no evidence of kidney damage The serum proteins were normal also

There are two complications of the initial or primary infection which may occur without noteworthy signs or symptoms The first is pleurisy with effusion Sometimes as in tuberculous pleurisy with effusion there may be scarcely any associated systemic symptoms The amount of fluid usually is only moderate

and fails to produce symptoms or be detected by physical examination Sometimes one entire pleural cavity may fill and cause marked respiratory embarrassment (Fig 6)

The other complication is the development of single usually, or multiple, rarely pulmonary cavities (Fig 7) There are generally no accompanying physical signs warning that a cavity has formed Frequently the cavity will appear after the acute symptoms have subsided but as has been mentioned apparently the cavity develops in one of the areas of consolidation The cavity may develop in a patient with inapparent infection The only sign present in many patients with coccidioidal cavities is occasional moderate hemoptysis generally on exertion With close roentgenological check of primary infections these cavities are observed to form and to close spontaneously Persistent cavities legacies of older infections generally are diagnosed on investigation of hemoptysis or in routine chest surveys

The hemoptysis alarming but so far as is known never severe enough to endanger life or even produce anemia may be incapacitating in an occupational sense There is rarely any fever malaise or other toxic manifestation of activity of the infection when hemoptysis occurs

Disseminated or Progressive Coccidioidomycosis Coccidioidal Granuloma

The signs and symptoms of disseminated or progressive coccidioidal infection naturally depend on the sites of the localization Practically all organs have been reported as having been involved Verrucous skin lesions are seen frequently in fulminating cases (Fig 10) They may occur on the face, scalp extremities or trunk and generally bespeak miliary dissemination

Often subcutaneous abscesses scatter over the entire body The diameter of the abscess may range from a few millimeters to twenty or thirty centimeters containing from a few minims to several ounces of pus frequently sanguinous The lesions may be very superficial or be deep and also involve bone They have very slight inflammatory reaction and are typical cold abscesses Generally the course in these patients is rapid also although Caucasians not infrequently rally and may actually recover

Bones and joints often are involved singly or more frequently in several sites One frequent location is the ankle although any bone from the skull to the metatarsals or phalanges may be infected

Coccidioidal salpingitis with or without peritonitis also occurs Like coccidioidal peritonitis in males the course in white frequently is very favorable The clinical picture and even the findings at operation are indistinguishable from tuberculosis The mimicry of tuberculosis is further seen in central nervous sys

tert coccidioidomycosis The most frequent involvement is that of the meninges Coccidioidal meningitis probably is the most frequent single cause of coccidioidal deaths in Caucasians Meningitis as part of miliary coccidioidomycosis runs a rapid course However the lesions may be few and basilar Unfortunately, they



Fig 10 Verrucous skin lesions of disseminated coccidioidomycosis in a fatal case

always seem to result in blocking the cerebrospinal fluid Where the patient does not die from extensive meningeal infection he succumbs to internal hydrocephalus The pressure often produces neurological findings suggesting localized brain or spinal cord lesion A few instances of localized granuloma of the brain and cord diagnosed preoperatively as brain or cord tumor have been observed

As has been indicated miliary coccidioidomycosis with involvement of brain, lungs and viscera is clinically indistinguishable from miliary tuberculosis

Differential Diagnosis

As has already been mentioned very mild primary infections cannot be differentiated from the common cold More severe infections generally are diagnosed as influenza or pneumonia occasionally as tuberculosis or even lung abscess Headaches have been so severe that brain tumor or poliomyelitis have been suspected The pleural pains may be so sharp as to result in diagnoses of fractured ribs coronary occlusion cholelithiasis nephrolithiasis subdiaphragmatic abscess and even acute appendicitis The prodromal skin rash has been mistaken for scarlet fever measles or drug rash In the majority of cases in civilian practice the diagnosis of the initial infection without skin lesions is not made

The onset of erythema nodosum or erythema multiforme usually results in a proper diagnosis However, tuberculosis and other causes of erythema nodosum must be differentiated In endemic areas the greatest danger is that of attributing every case of erythema nodosum to *Coccidioides* At the same time that 432 San Joaquin Valley patients with coccidioidal erythema nodosum were seen 21 other patients were observed to have erythema nodosum due to other causes[11] Eleven were due to tuberculosis and 10 were caused neither by *Coccidioides* nor by *M tuberculosis* Patients with erythema multiforme have been diagnosed as eczema and even smallpox In view of the malaise chills fever and backache of the pre eruption phase and the distribution of the lesions on the palms of the hands upper extremities and face the smallpox error is understandable, especially when erythema nodosum is absent However since erythema nodosum usually is present and arthritic pains and phlyctenular conjunctivitis also are frequent associates this pitfall should be avoided

The differential diagnosis of the coccidioidal cavity involves considering tuberculosis and lung cyst the latter because there is usually so little reaction demonstrable in the roentgenogram While sometimes appearing above the clavicle most coccidioidal cavities are in the middle lobe or lower lobes

The differential diagnosis of the disseminated form also is very inclusive As has already been indicated the most difficult differentiation is from tuberculosis Meningitis is confused sometimes with encephalitis the equine variety being endemic in much the same areas Two sites of tuberculous involvement rarely occur in disseminated coccidioidomycosis Coccidioidal renal involvement unlike tuberculous nephritis has never been reported except in generalized infection when the entire body is riddled Only once has coccidioidal enteritis been reported Greaves [4] found two mucosal lesions one in the ileum and one in the jejunum in a Negro with miliary coccidioidomycosis Obviously it would not be possible to say whether the lesions were hematogenous or due to spherules in the intestinal contents

The problem of differential diagnosis may be summed up with the admission that on clinical grounds alone and even with roentgenographic evidence, too, it is impossible to diagnose coccidioidomycosis Differentiation either of initial or of disseminated infections must be obtained by laboratory proof

LABORATORY DIAGNOSIS

Incontrovertible proof of coccidioidal infection consists of demonstration of the sporangia spherules in tissue sections (Fig 9) or recovery of the living fungus In both procedures essential criteria must be met The tissue sections may be obtained from biopsies or autopsy material and thus are of aid only in establishing the etiology of disseminated infections Routine fixation and the usual hematoxylin and eosin staining suffices One must demonstrate the characteristic, double contoured spherules with endospores and without budding Because these criteria frequently are not met, at least two infections have been ascribed erroneously to Canada

Culture Methods

Living *Coccidioides immitis* can be recovered from sputum and occasionally from pleural fluid in primary coccidioidomycosis or in disseminated infection from pus spinal fluid or tissues in disseminated infection It is not sufficient to depend on a coverslip diagnosis of sporangia In pus abundant with typical spherules the diagnosis may be practically certain but even then only when the examination is made by a person familiar with the organism It is really necessary that the identity be established by demonstration of the typical, white, cottony fungus on culture (Fig 1) and the characteristic spherules (Figs 3 and 4) in inoculated laboratory animals

Practically any culture medium is suitable Sabouraud s medium is very satisfactory unless there is a heavy contamination Bacteria and especially other fungi frequently overgrow *Coccidioides* A differential medium on which *Coccidioides* will grow only scantily but which rarely will support any growth of bacteria or other fungi from specimens of animal origin consists of 1 per cent ammonium chloride 1 per cent sodium acetate 0 8 per cent tribasic potassium phosphate 2 per cent agar autoclaved at fifteen pounds pressure for ten minutes Just before pouring into Petri dishes add 0 04 per cent cupric sulfate Unfortunately other organisms from the soil will multiply on this medium so its usefulness is restricted in attempting to study the distribution of *Coccidioides* in nature

A satisfactory procedure is to culture suspected material on Sabouraud s medium and the differential diagnostic medium described in the previous para

graph One should incubate cultures a week examining the differential medium especially carefully before discarding them as negative If a suspicious growth appears a loopful should be shaken up in 1 c c of normal saline and injected intraperitoneally into a white mouse or intratesticularly into a guinea pig Tager has advocated intranasal instillation in several mice but if a massive dose i inoculated intraperitoneally a mouse will die in ten to fourteen days with lesions scattered throughout the lungs and frequently in the omentum, spleen or at the point of inoculation The danger of laboratory infections is especially great when cultures are handled As Tager points out in the usual diagnostic bacteriological laboratory the use of the intranasal route would be risky

Combined culture and animal inoculation of a specimen enhance the possibility of recovering the fungus If a specimen is heavily contaminated as in any sputum specimen, it should be treated with 0 05 per cent final concentration copper sulfate before the animal is inoculated The fungus does not survive alkali acid or other concentration methods used for *M tuberculosis* and this copper sulfate treatment permits recovery either of *Coccidioides* or of *M tuberculosis* After allowing several hours of contact with the copper the material is centrifuged and the sediment cultured on a blood agar plate The specimen is refrigerated until the following day If the blood agar plate shows little growth the specimen is inoculated If there is heavy growth it is recultured Even if contamination is heavy on the third day the material is inoculated The sediment is suspended in 1 c c of saline and injected intratesticularly in a guinea pig If *Coccidioides* is present orchitis usually develops within a week or ten days However it is generally best to wait a month before sacrificing the animal

Sputum examination of primary infections often is impossible since frequently the patients do not cough up sputum At times the fungus has been recovered from stomach washings However one should examine stomach washings promptly as the fungus may soon be digested

Coccidioidin Test

One of the most valuable aids to diagnosis is the *coccidioidin* test Coccidioidin has been made in various ways [6] The material which has been prepared at the Stanford School of Medicine consists of ten strains of *Coccidioides* grown for a month and a half to two months on asparagine synthetic medium The formula is that used for producing the tuberculin of Purified Protein Derivative except that 2½ per cent glycerol is used The constituents are 1 asparagine 14 00 dipotassium phosphate C P 1 80 sodium citrate C P 0 90 magnesium sulfate C P 1 50 ferric citrate U S P VIII (scales) 0 30 dextrose to grade known as cerelose 10 00 glycerol C P 5 00 water to make 1000 00 The

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in states from Missouri to western New York and Pennsylvania and as far south as Tennessee show equivocal and occasionally a definitely positive reaction to coccidioidin before they could possibly have acquired coccidioidal infections in endemic areas [?] It suggests the possibility that these people may have been infected by some other fungus with which coccidioidin carries a slight cross sensitivity much as *Haplosporangium* antigen does to coccidioidomycosis The recently recognized complicating factors still do not detract from the usefulness of the test any more than Aronson s[1] demonstration of cross sensitivity of abortus protein derivative and derivatives of various non pathogenic acid fast organisms to tuberculin eliminate the value of the tuberculin test Incidentally Aronson[1] thoroughly disproved the possibility of cross sensitivity between *M tuberculosis* and *C immitis*

Serological Tests

Serological tests recently have proven of considerable diagnostic and prognostic value The procedures have not yet been published because of persistent difficulties with antigen Using coccidioidin as antigen it has been possible to demonstrate precipitins and to fix complement In inapparent or very mild primary infections these humoral antibodies are rarely demonstrable Generally the more severe the infection the higher the titer particularly in complement fixation Patients with progressive disseminated infections usually have complete fixation in serum dilutions of 1 16 to 1 256 or even higher However they may have no precipitins In the severe initial infections precipitins often are demonstrated to an antigen dilution of 1 40 or even 1 200 A patient with a primary infection which first produced only precipitins but whose serum later fixed complement in progressively higher titers would be suspected of impending dissemination The precipitins appear a few days after sensitivity to coccidioidin develops As has been indicated complement fixation usually is demonstrable a little later However precipitins generally diminish after a few weeks and vanish in a month or two Occasionally they may persist for several months The higher the titer of complement fixation the longer it tends to remain After severe infections fixation may continue for several years The serological tests may be applied successfully to pleural fluid and even cerebrospinal fluid In the patients with few meningeal lesions and in which the symptoms are largely due to mechanical cerebrospinal blockage the serological tests usually are negative

Blood Changes

As Wyckoff and Usigli have shown in initial coccidioidomycosis there is frequently but not necessarily a moderate leukocytosis to between 10 000 and 16 000

time period for growth has been determined by potency tests Aqueous merthiolate is added to a final concentration of 1 10,000, and the material is Berkefeld filtered Sterility tests potency tests on sensitive humans and specificity tests on normal humans are made The coccidioidin is diluted to 1 100 concentration for routine testing While it is necessary to dilute to 1 1,000 or even 1 10 000 to avoid uncomfortable reactions in sensitive persons like erythema nodosum or multiforme patients there is no danger of lighting up a quiescent focus or causing a dissemination of a primary infection even though a severe local reaction occurs Also there may be a systemic reaction and even recurrence of erythema nodosum without any permanent deleterious effect Coccidioidin more concentrated than 1 100 may cause non specific reactions[1] However even 1 10 coccidioidin may not suffice to evoke a reaction in a patient with disseminated infection The diluted coccidioidin will retain its potency for at least a month if it is not contaminated The undiluted material maintains its potency for at least five years even when not refrigerated The test is made as is the Mantoux test administering 0 1 c c intracutaneously It generally reaches its peak at approximately thirty six hours It should be read as is the tuberculin test counting only induration which measures at least 5 mm in diameter

As already indicated the significance is much the same as that of tuberculin Failure to react eliminates the possibility of coccidioidomycosis unless the infection is just beginning or unless the patient has a disseminated infection and is anergic In the former condition the repetition of a test in another week with a positive reaction establishes the diagnosis unequivocally In the latter state it should be very easy to demonstrate the living fungus by examining appropriate material A positive reaction merely informs us without relation to time that infection has occurred The size of the reaction is no indication of the time when the infection occurred Violent reactions have occurred ten and even twenty five years after people have left endemic areas As has been indicated above, demonstration of a change from a negative to positive test is almost as diagnostic as recovery of the fungus

Emmons[18] has reported cross sensitivity to a similar antigen made from *Haplosporangium parvum* a fungus which he has recovered from Arizona rodents in patients *sensitive to coccidioidin* This raises the question of whether some persons sensitive to coccidioidin have been infected with *Haplosporangium* However at least in the San Joaquin Valley sensitivity to coccidioidin is much greater than to *Haplosporangium* antigen Moreover difficulty in producing infections in laboratory animals with *Haplosporangium* makes one wonder whether the fungus actually infects man More information will be necessary before *Haplosporangium* infection can be judged to incriminate the significance of the coccidioidin test Nevertheless some cross sensitizations do exist Many people

The roentgenographic appearance of disseminated coccidioidal infections has been described by Carter[9] There may be extensive pulmonary involvement, frequently with miliary lesions However even with extensive skin and subcutaneous lesions the pulmonary roentgenogram may show an apparent healing process and frequently no evidence whatsoever of the infection The roentgenographic appearance of individual coccidioidal bone lesions is usually indistinguishable from tuberculosis although by and large there is a greater tendency to new bone formation Moreover the frequency of multiple bone lesions especially prone to involve an ankle or the thoracic cage, is another differential clue

The roentgenographic diagnosis of coccidioidomycosis is best summed up in an anecdote credited to Edward Chamberlain who when on a return visit to San Francisco was shown a film and asked for his diagnosis Without hesitation he is said to have replied coccidioidal granuloma The substance of his explanation for this brilliant diagnosis is as follows The film is typical of tuberculosis but you would not have shown it to me if it were simple tuberculosis Therefore it had to be coccidioidal granuloma

Prognosis

The prognosis of primary coccidioidomycosis including the patients with coccidioidal cavities is excellent Probably not more than one tenth of one per cent of the primary cases disseminate Obviously the outlook for females is better than for males Caucasians are much better off than the dark skinned races

When dissemination occurs the prognosis is grave The figure generally given for eventual recovery is approximately 50 per cent In all likelihood it is really less since no doubt some of those cases actually were primary

Prevention and Treatment

There seems little possibility of preventing infection Possibly when we discover where the fungus grows in nature steps may be taken to eradicate it However in view of the vast areas involved probably this will be impractical That the fungus is wafted about in the dust has been indicated already Therefore attempts to lay dust are theoretically advantageous However the extent of *dust storms in endemic areas also makes this procedure seem doomed to failure*

If there is little likelihood of preventing infection then we should consider measures to prevent the infections from disseminating As has already been mentioned *the evidence is strong that dissemination nearly always occurs relatively* soon i e within the first few months after the initial infection There is reason

There is not usually a change in the proportion of leukocytes to lymphocytes but there is generally a preponderance of immature leukocytes. Frequently there is an eosinophilia ranging from 4 per cent to 20 per cent and even higher. In the healing stages the proportion of lymphocytes usually rises sometimes to 50 per cent of the total and the shift to the left in the leukocytes disappears. These changes are missed in the usual blood count and are demonstrable only when very careful and repeated examinations are made. The differential count does have prognostic value in following the course of the infection.

Of greater use in diagnosing coccidioidomycosis and following the course of healing is the *erythrocyte sedimentation test*. It is of especial value in interpreting the significance of a positive coccidioidin test. Patients with active coccidioidal infection whether primary or disseminated show accelerated sedimentation. Thus, a normal sedimentation rate in a patient with a positive coccidioidin makes it unlikely that a current illness is coccidioidal. An accelerated rate does not establish the infection as currently active but indicates that the possibility exists. Further steps should be taken to prove or eliminate it. As a primary infection is focalized the sedimentation rate approaches normal. The test may be used to supplement other criteria in permitting activity of a patient. The fact that most patients with old coccidioidal pulmonary cavities have normal sedimentation times is further evidence that these lesions are not active, even though the fungus may be present in the sputum.

Roentgenography

Roentgenograms may be of considerable diagnostic importance[7,8,9,3]. However as has already been indicated most inapparent infections have no accompanying demonstrable pulmonary lesions. As we have seen such lesions as do appear may be exceedingly variable. There may be multiple circumscribed densities resembling metastatic malignancy single or multiple densities like bronchopneumonia or primary tuberculosis densities resembling lobar pneumonia or wedge shaped densities which look like those of epituberculosis[12]. There may be considerable hilar lymphadenopathy. Both Carter and Winn have emphasized hilar enlargement as indicating likelihood of dissemination, although many persons have such findings and do not disseminate. The occurrence of pleural effusion has been mentioned already. The characteristic thin wall i e no roentgenographic evidence of reaction in coccidioidal cavitation and its resemblance to lung cyst have been discussed already. It will be recalled that as the coccidioidal lesions heal they may calcify apparently resulting in a roentgenogram indistinguishable radiologically as well as pathologically from the primary tuberculous complex.

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Sept 1 1943

CHAPTER XV

TRENCH FEVER

By RICHARD P. STRONG

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Introduction

Definition—Trench fever may be defined as a specific infectious febrile disease in which the virus is present in the blood and sometimes in the urine and is commonly transmitted from man to man by the body louse Pediculus humanus. There are usually enlargement of the spleen and an eruption consisting of small erythematous spots or papules, headache, dizziness, pain in the legs especially the shins, the back and behind the eyeballs, injection of the conjunctivae and a sharp rise in temperature to 103° or 104°F. In the majority of the cases the fever or other symptoms assume a relapsing character. No single symptom or characteristic of the disease yet recognized is pathognomonic.

Synonyms—An identical or similar disease has also been described by different authors and in various localities under a variety of other names. Thus references are found in medical literature to a similar disease described as Volhynia fever, quintan or five days' fever, Polish fever, Russian intermittent fever, Meuse fever, His-Werner disease, gaiter pain fever, shin fever

trench fever infectious periostitis shank fever and Salonica fever However it is by no means clear that in all of these instances trench fever is always referred to and in some of them there seems to be the probability particularly in connection with their etiology that other fevers have been described or confused with trench fever and sometimes included with it Some of the diseases thus described have sometimes suggested and apparently included mild forms of typhus European relapsing fever mild Weil s disease or even paratyphoid fever

History

Trench fever is one of the infectious diseases regarding which our knowledge has been obtained as a result of the recent war It has been suggested that as the disease was unrecognized or unknown before the war it had been introduced by colonial troops into the armies in northern Europe where it attracted particular attention by its prevalence or again that as the armies in the field were more or less exposed to medieval conditions, hence a return to medieval diseases hitherto imperfectly known might be expected One can only conjecture as to whether the quintan fever described by Hippocrates Galen and Razes was the disease known today as trench fever Clinically the disease might in earlier years frequently have been mistaken for malaria or European relapsing fever As there is no specific diagnostic laboratory method known for trench fever even today it is probably often confused with other diseases Cases of trench fever might sometimes very easily be confused with influenza modified paratyphoid fever malaria European relapsing fever dengue phlebotomus fever or mild epidemic jaundice It has been suggested that trench fever might be analogous to the sweating sickness of the Middle Ages and severe sweating as a consequence of which the bedclothes were often soaked has been noted by various observers but if one compares trench fever with the descriptions of either the sweating sickness or the Picardy sweat which was reported to have first appeared north of the Somme and in Flanders it is seen that there is little or no resemblance between them

However the identity of sweating sickness as thus described with military fever as it occurred at least in some outbreaks has never been definitely determined Thus Michael Foster[1] emphasizes the fact that in some of the French epidemics the mortality has frequently been so low that it is difficult to reconcile this disease with the lethal pestilences of sweating sickness of Tudor times However it does not seem entirely improbable that miliary fever as observed in certain outbreaks may have been a somewhat analogous disease to trench fever though this analogy is by no means definite

As to the suggestion that the disease may have been introduced into Europe by colonial troops it may be said that trench fever does not definitely correspond at least to any of the well recognized exotic forms of fever Experiments have shown that trench fever is evidently different from pappataci fever and it is a much severer disease although it is in some respect analogous to pappataci fever Dengue fever is not invariably accompanied by a skin rash but the rash is generally observed and is a very striking feature of the disease Such a rash has never been observed in trench fever Also the relapsing type of fever observed in trench fever does not occur in dengue The differential leukocyte count is also different in the two diseases

Seven-days fever of India has a similar method of onset and also some clinical resemblance in that there are severe headache pains in the back and limbs and pyrexia of a saddle back type occasionally of a continuing type and the spleen is sometimes enlarged but in seven-days fever the temperature falls to normal about the seventh or eighth day after the second rise and the eruption when present is different Moreover Ido[2] has shown that this disease is caused by a spirochete

In double continued fever the period of initial pyrexia is said to last for about ten days to a fortnight and then after an interval of from three to seven days of relative or absolute apyrexia a second wave of ten days of fever follows This disease also differs in other respects from trench fever

Van der Scheer has described a five days fever which is said to be associated with an eruption of red macules and papules about the size of a pin s head occurring on the chest back and abdomen After a five days remittent fever the crisis occurs on the sixth or seventh day when the temperature falls to normal In other respects the disease does not particularly resemble trench fever as we know it today

The disease known as Colombo fever" has been observed particularly in Ceylon and recently in Serbia In this disease there is a continued fever of a mild type resembling paratyphoid occasionally showing several relapses which resemble undulant fever An organism bacillus colombensis found in the stools is said by Castellani to be associated with it No roseola or other rashes have been noted in the disease and the spleen is seldom palpable

Trench fever also cannot be definitely identified with any of the other described but imperfectly differentiated fevers of the tropics but it must be borne in mind that a number of these have not been carefully investigated

The Epidemic of 1915–1918

During the latter part of 1915 and in 1916 the occurrence of a disease characterized by febrile relapses became gradually recognized in some of

the armies in northern Europe It was first referred to in Flanders and France by Graham and Hunt and Rankin McNee Brunt and Renshaw first described it under the name of trench fever Herringham also called particular attention to the disease and stimulated its further study His and Werner described cases of a similar disease in German or Austrian troops in Volhynia and Poland

McNee Brunt and Renshaw[3] did much to establish the specificity of the disease and were able to demonstrate that the infectious agent was present in the blood and that the disease could be transmitted from man to man by direct inoculation of the blood

There was much speculation also as to the nature of the infectious agent and the method of spread of the disease The disease was supposed by some to be spread by rats or mice Just as in the case of malaria and yellow fever before the proof of their method of transmission was demonstrated so in trench fever a number of observers had suggested the disease was spread by insects Flies mosquitoes fleas and lice were all suggested as being concerned in the transmission of the disease

Davies and Weldon allowed themselves to be bitten by lice immediately after they had fed on trench fever patients the lice having been originally collected from soldiers One of them developed trench fever twelve days later Werner and Kuczynski also reported they had developed Volhynia fever after being bitten by lice Werner had suffered from Volhynia fever six months before however none of these experiments was properly controlled Pappenheimer and Muller also apparently succeeded in transmitting the disease to one of three volunteers but this patient was suffering from a complicating femoral phlebitis Among those who published in favor of the idea that the disease was conveyed by vermin were Hirst Hughes Hunt and McNee Grieveson and Davies and Weldon Among those who were opposed to this idea or believed the disease to be spread in another manner than by lice were Muir Costello Hunt and Rankin Dyke Ramsey Sundell and Nankivell Graham Houston and McCloy Darling and Wilson Chambers Chandler O Connell and Wright Sundell and Nankivell[4] in an admirable summary of our knowledge of trench fever at the time published March 16 1918 after considering all the evidence above referred to in relation to the spread of the disease stated that "Considering the evidence for and against the propagation of trench fever by means of lice we can only say that transmission by lice is not proved There is as yet no evidence that lice can pass on this disease if the mechanical factor is eliminated"

In October and November 1917 the writer being cognizant of the enormous loss of man power which the disease was causing in some of the allied armies and of the great danger of its introduction and increase in other armies made a formal offer to attempt to determine definitely and

with properly controlled experiments the method of transmission of the disease which obviously was the most important problem in connection with its prevention This offer was accepted and after the necessary authority had been obtained from the American and British military authorities in January 1918 and the writer had secured the detail of six other medical officers two non commissioned officers from the American Expeditionary Forces and one medical officer from the British Expeditionary Forces (the names of the members of the Commission that carried out these investigations were Homer F Swift Eugene L Opie Ward J Macneal Walter Baetjer A M Pappenheimer A D Peacock and David Rapport in addition to the writer) to assist in carrying out these investigations as well as a detail of eighty six enlisted men from the United States army who had volunteered to submit to the necessary experiments the work was undertaken

At the same time the British War Office also appointed a commission to study trench fever in London with Surgeon General David Bruce as chairman and Major W Byam as supervisor of the clinical and experimental work The other members of this Commission were Mr Bacot Lt Col Harvey Professor Plimmer Lt Col French J A Arkwright Sir P M Fletcher and Lt A F Hurd

In the work of each of these two commissions there was close and friendly cooperation The British Commission carried out its work in London upon civilian volunteers and in well equipped laboratories while the American Commission carried out its investigations in improvised laboratories in the field The latter commission however had the advantage of securing young and healthy volunteers from the United States army for the experiments and a plentiful source of supply of acute cases of trench fever

Practically all of the important knowledge we possess regarding trench fever is to be found in the two reports of these commissions [6] In the present article obviously only a summary of our knowledge of this disease can be given

Geographical Distribution and Prevalence During the World War

The disease was observed during the war particularly in troops in Flanders France Poland Galicia Bukovina Italy Salonica Macedonia Mesopotamia and Egypt A few cases apparently originated in England Certain areas within these countries were particularly infected The disease was one of the largest sources of wastage of man power in the combatant forces From 1915-1918 it has been estimated that it was the cause of from one fifth to one third of all cases of illness in the British armies in

spent three days upon one subject infecting him after which after an interval of thirteen hours they were transferred to a second subject for three and a half days more infecting him then after fourteen hours being transferred to the third subject for four days and a half also infecting him and then after an interval of fifteen hours to the fourth subject also infecting him thirteen days from the time they had last bitten a case of trench fever The incubation periods of these cases were fifteen fifteen fourteen and thirty days respectively These experiments all show that the transference of the infection by the louse is certainly not accomplished simply by a mechanical transference of the virus and they point to a multiplication of the virus or an intermediate life cycle of the organism within the louse There is also no evidence from these experiments that the louse is infective until six or seven days from the time of first biting a trench fever case and it is known that the louse does not retain the remnants of its food ordinarily for a longer period than several hours excreting it with its next meal This is very suggestive of a cycle of development within the louse and not a mere mechanical transfer of the virus from individual to individual by this insect a condition found with the insect transmission of known protozoal infections rather than with bacterial diseases

In eight experiments with volunteers it was shown that trench fever may be produced in an artificial manner by scarifying the arm and rubbing in as in vaccinating against smallpox a small amount of the excrement of lice which had fed upon trench fever cases The British Trench Fever Commission first demonstrated this method of infection the excreta being collected from the sixth to the nineteenth day after first feeding upon the patient In these instances it was found that the incubation period of the disease varied from seven to eleven days

Incubation

The incubation period of the disease in nature probably varies between ten to thirty days though if the infection is acquired from a very large amount of the virus this period may be somewhat shorter In the cases in which the disease was produced by artificial methods of infection such as the intravenous injection of blood or one of its constituent elements or by scarifying the skin and rubbing in the virus either in the louse excrement or in the urinary sediment the incubation has usually varied from five to twenty days and with lice living under practically normal conditions from fourteen to thirty days During the incubation period the patients sometimes show prodromal symptoms shortly before the onset of the attack of fever consisting of malaise headache and pains in other parts of the body

PATHOLOGY

The disease constitutes a mild specific form of septicemia and the symptoms of it are obviously due to the action of the toxins of the virus which circulates in the blood and is excreted at least partially in the urine. The virus may sometimes persist in the circulating blood for as long a time as 300 days from the beginning of the disease, as was demonstrated by the British Commission. In chronic cases the toxins of the virus give rise to a more or less cachectic condition. As there are no records of autopsies in *trench fever cases, the disease being practically never fatal, no histological* investigations have been carried out except in connection with the maculae of the skin. Schmunke[13] has shown that the corium of the trench fever macule is hyperemic and edematous, and that there is a perivascular lymphocytic infiltration with a variable number of polymorphonuclear leukocytes. The skin lesions differ from those seen in typhus fever in that there are no necrosis of the endothelial cells of the vessel wall and no hyaline thrombosis. It has been suggested that the segmental area of cutaneous hyperesthesia may arise from inflammatory changes in the dorsal nerve roots.

CLINICAL FEATURES

The most characteristic clinical features of trench fever are the sudden onset, accompanied by headache, dizziness, pain in the legs, especially the shins, the back, and behind the eyeballs, particularly when moved, nystagmus on turning the eyes completely sideways, injection of the conjunctivae and a sharp rise of temperature to 103° or 104° F. The fever in over one half of the cases subsequently assumes a relapsing character. Enlargement of the spleen and the appearance of small erythematous spots or papules occur in from seventy to eighty per cent of the cases. The erythematous spots are observed particularly over the chest, back and abdomen. They are usually not raised above the surface of the skin, are pink in color, disappear on pressure and generally measure about two to four mm., although sometimes they may measure from four to six mm. in diameter. Occasionally the rash is distinctly papular in character. In number the spots vary from several to one or two hundred. They often disappear in less than twenty-four hours after their appearance, and they may occur as early in the fever as on the second or third day, or be first observed just prior to or during a relapse. While no one of these symptoms given above can be regarded as characteristic or constant, the presence of several or all of them usually serves to make an accurate diagnosis of trench fever.

The urine often shows a trace of albumin, but evidence of true nephritis

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increase in pulse rate Whether these signs indicate an actual change in the size of the heart or not is questionable but at least they indicate a distinct *alteration in the condition of the heart*

Occasionally a picture somewhat resembling paroxysmal tachycardia is seen during the course of trench fever Precordial pain and hyperesthesia are not infrequently observed Accompanying these symptoms and signs directly referable to the heart there is at times dyspnea even with the patient in bed It is also not an infrequent symptom when the patient is up and about However as these symptoms and signs are also found with certain other infections they cannot be regarded as peculiar to trench fever

Areas of tenderness are frequently associated with the pains in the head legs and back already referred to and may involve skin muscles tendons bones or joint cartilage *although the nerve trunks themselves* do not appear to be involved The area of skin found by the British Commission to be most hyperalgesic was that running from knee to ankle along the *outer border of the tibia Byam and Carmalt Jones found that the areas* of skin tenderness seem to correspond to the eighth cervical first and seventh dorsal and the first to fifth lumbar segments of the cord The whole of these segmental areas were involved in comparatively few cases those most commonly involved being the lower segments of the lumbar group Sundell[8] showed that areas of analgesia might be detected in some of the more prolonged infections the loss of sensibility varying in degree from a mere blunting of sensation to complete analgesia The most common situations for this phenomenon were the outer surface of the calf the infrapatella the scapula and deltoid region With reference to these pains and areas of tenderness it is interesting to refer to the cases in the later stages of the disease described by Rudolph[9] and Soltau[10] under the term of trench fever cachexia Soltau found that not less than seventy per cent of cases diagnosed in the British army as myalgia were really suffering from trench fever Lloyd[11] also describes subacute cases of trench fever diagnosed as rheumatism myalgia or neuritis

Chronic Cases

The British Commission found that in a large proportion of the cases of trench fever invalided to England there is a tendency to advance through a subacute towards a chronic condition with symptoms of disorganized action of the heart and in some cases symptoms of neurasthenia The symptoms met with in these cases were summarized in the order of their importance as follows exhaustion giddiness and fainting headache breathlessness on exertion pain irritability lassitude sweating coldness of the extremities palpitation and cardiac irregularity fever The majority of the chronic

is not present in the uncomplicated disease In a small percentage of the cases frequent desire of micturition is complained of, which Byam has shown is due to polyuria The leukocyte count is very variable There is frequently a leukocytosis and the leukocytes may rise at the time of the relapse In other cases however the count may be normal or there may be a leukopenia It has been suggested that in patients with persistent pain in the shins a steady high count probably indicates a continuation of the infection

The fever does not always follow a definite type but may consist of first a short attack lasting for about a week with sometimes but not always after a few days a single short rise second a more prolonged initial fever sometimes lasting for six or seven weeks with relapses not distinctly marked and third a more regularly relapsing fever with more or less definite normal intervals lasting from five to seven days Many variations in these types of fever are seen and in some of the patients there may be a long fever lasting from forty to sixty or more days with only very slight remissions

It has been shown by the experimental transmission of trench fever through several generations in man either by means of the direct inoculation of the infected blood or through the agency of infected lice that all these main types of fever are common in this disease and moreover that the type of fever which appears in an inoculated case does not necessarily conform to the type observed in the original patient from which infected blood was taken

The number of relapses varies greatly from three to five periods are common and some have as many as six or seven relapses Several of our patients who had been entirely free from fever for from six to seven weeks or longer developed typical relapses In these cases reinfection could be definitely excluded In some of the cases at the time of the relapse the temperature may remain normal but a marked increase of the pulse occurs and other symptoms of the disease appear Occasionally relapses persist as late as a year or more after the original attack

Tachycardia and the condition known as D A H (disordered action of the heart) of soldiers have been described as frequent complications or sequelae particularly in cases of the disease occurring in soldiers attacked while performing heavy military duty or in those returning to such duty before completely well Carmalt Jones[7] has found that among 100 cases of disordered action of the heart taken at random and serious enough to reach a heart center two out of three were due to trench fever alone and eight out of nine were due to this infection at least in part In a group of patients Swift noted the position of the apex impulse from day to day and on several occasions observed the shifting of the apex impulse from well within the nipple line to an inch or more beyond it Also the area of cardiac dullness had apparently increased in width Concomitant with this change there had been a distinct

increase in pulse rate. Whether these signs indicate an actual change in the size of the heart or not is questionable but at least they indicate a distinct alteration in the condition of the heart.

Occasionally a picture somewhat resembling paroxysmal tachycardia is seen during the course of trench fever. Precordial pain and hyperesthesia are not infrequently observed. Accompanying these symptoms and signs directly referable to the heart there is at times dyspnea even with the patient in bed. It is also not an infrequent symptom when the patient is up and about. However, as these symptoms and signs are also found with certain other infections they cannot be regarded as peculiar to trench fever.

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cases presented all of the above symptoms Byam believes that considerable evidence exists which points to a specific action on the vagus in such cases

Differential Diagnosis

While there is no specific laboratory method of diagnosis for trench fever laboratory examinations are often of assistance in differentiating this disease from other infections such as malaria European relapsing fever tick fever, seven days fever and Weil s disease without jaundice Here it may be merely stated that neither spirochaetae nor the leptospira ictero hemorrhagica has ever been encountered in undoubted trench fever cases that the general character of the disease and particularly the relapsing character of the fever and the nature of the rash are quite different from what has been observed in typhus From typhoid and paratyphoid fever it may be distinguished by the absence from the blood stools and urine of trench fever cases of organisms of the enteric group Marris[1] insists that the atropin test is of value in differentiating trench fever from the enteric group since the toxins of trench fever stimulate while those of enteric depress the nervous system

The absence of marked catarrhal symptoms usually (though not always) serves particularly to differentiate the disease from influenza while the character of the rash and the differential leukocyte count serve to distinguish trench fever in the early stages of the disease from dengue fever In epidemic jaundice not only the presence of the leptospira icterohemorrhagica but the nephritis and usually the jaundice serve to distinguish this disease from trench fever Pain in the muscles of the neck in trench fever may at times be so severe as to resemble the neck pains of meningitis and the abdominal pain may simulate that of appendicitis so that cases of this disease have been operated upon for appendicitis by mistake However the abdominal pain of trench fever is elicited by superficial palpation rather than by deep firm pressure and as a rule there is no confusion between these two conditions Undulant fever obviously may be differentiated from trench fever by the detection of the micrococcus melitensis in the blood or by the agglutinating reaction of the serum with this organism

Prognosis

The importance of the disease has particularly depended upon its wide prevalence heart complications and great loss of service caused by it during the war Generally the prognosis in properly treated cases is good and the

disease is practically never fatal. It has been estimated that of men in good health at the time when afflicted with the acute disease about 85 per cent were ready for return to duty in two months from the time of onset. However, this statement does not apply to the subacute or chronic cases, and the occurrence of subsequent relapses in some of the 85 per cent of recovered acute cases cannot be excluded. Of 236 advanced cases of the disease treated at Hampstead, England, giving an average disability of 4.5 months, only 6.2 per cent left the hospital free from symptoms, while 7.2 per cent were returned to civil life as permanently unfit. Of those discharged from the hospital after nine months, 60 per cent had still shown greater or less evidence of the persistence of the disease during the time since their discharge. In relation to prognosis, the immediate placing of the patient at rest in bed at the time of onset and during all active symptoms of the disease is important. In the subacute and chronic stages a steady gain in weight is said to constitute the most reliable guide to a favorable prognosis. Men below thirty-five years of age are more likely to entirely recover in a shorter period of time than men above that age.

PROPHYLAXIS

Exceedingly great care should be taken to completely disinfect all patients as soon as practicable and particularly upon their entering the hospital. Patients on entrance should be carefully bathed and subsequently sponged with alcohol with the object of removing the virus from the skin. Since both varieties of pediculus humanus, P. corporis and P. capitis, may convey the disease, careful disinfestation of the hair should be carried out. It must be borne in mind that while a temperature of 55° C. for 30 minutes destroys the louse P. humanus and its ova, such a temperature does not suffice to destroy the virus of trench fever which may be present upon the underclothing of trench fever patients. For the destruction of the virus of trench fever a temperature of 70° C. of moist heat is sometimes necessary. The clothing of patients upon entrance should be removed and both clothing and blankets, whether or not lice or ova are found upon them, should be carefully sterilized by moist heat at a temperature not below 70° C. for 20 minutes, since it is possible for the virus to be still present on the clothing. It should be borne in mind that a man with trench fever may be entirely free from lice at the time that he develops symptoms of the disease.

Those handling the sick and their discarded garments should take special precautions to avoid becoming infested with lice. Louse-proof overalls and rubber gloves are desirable for attendants. It has been shown

that the virus of trench fever in excreta of lice may retain its virulence for at least four months Bed linen before washing may be immersed in a 2 per cent lysol or cresol solution for 20 minutes which destroys the virus

Trench fever patients should at all times be carefully protected from louse infestation and inspection of them for lice should be made daily since it has been shown that sometimes even as late as the 300th day of disease a patient s blood may remain infective and be capable of infecting lice They should be treated in separate wards

As the urine may contain the virus and be infective it should be sterilized during the active stages of the disease Infection with the virus may occur through the conjunctiva and 0 1 milligram of infective louse excreta has produced trench fever when inoculated subcutaneously Infection probably does not take place by the mouth or by inhalation Sputum cups should be provided for patients and as the sputum may be infective it should also if present be sterilized

The immunity in relation to the disease is variable and one attack does not necessarily protect The British Commission showed experimentally that re infection was possible in two instances on the 132nd and 198th day after onset

An eradication of lice results in an eradication of the disease

TREATMENT

Up to the present time no specific remedy for the disease has been found Sweet and Wilmer and Richter have reported favorable results from the intravenous injection of 10 c c of a 1 per cent solution of collargol but these observations have not been further confirmed The British Com mission also employed intravenously a large number of drugs such as acriflavine galyl collosol argentum iodin antimony collosol sulphur manganese palladium colloidal rhodium intramine kharsivan eusol trypan red tartar emetic and disodoluargol but without favorable results

The efforts of the physician during acute stages of the disease should be directed towards maintaining the patient s nutrition and relieving the pains when they are so severe or persistent as to interfere with rest Phenacetin and aspirin 0 3 gm of each usually have sufficient analgesic and antipyretic action to relieve temporarily unpleasant symptoms Good food and com plete rest are probably the best remedies to help the patient develop the necessary immunity to overcome the infection The proper direction of convalescence is probably the most important part of treatment The pulse rate should be as carefully recorded as the temperature and other symptoms or signs of the disease should be carefully watched for

As long as two or three of the positive signs of the disease persist one should regard the infection as still active. The patient should not be allowed to get up and be about until it is evident that the infection has been entirely overcome. As a rule it is advisable not to allow the patients up until they are well past the time of an anticipated relapse. The time which the patient is allowed to be up should be progressive, beginning with a few hours at a time. If during this increase of exercise there is unusual tachycardia or return of any of the symptoms, the time of sitting up should not be increased and if these symptoms persist the patient should be returned to bed. After the patient has been allowed to be up all day without unfavorable symptoms he should be placed on a course of graded physical exercise. The striking feature of trench fever is its tendency to relapses, and during these recurrent relapses the patient should always be kept in bed.

The treatment of the chronic disease consists briefly in attempting to improve the general health and hygienic conditions of the individual, with particular attention to rest, exercise, diet and climatic conditions.

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CHAPTER XV-A

Q FEVER: COXIELLA BURNETII FEVER

By GEORGE BLUMER AND HENRY A. CHRISTIAN

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SYNONYMS AND TERMINOLOGY

It is always regrettable when a new disease receives a name which gives no clues to either its etiology or pathology, for experience has shown that a name once associated with a disease, even for a brief period, tends to stick. Originally Q fever was an abbreviation of Queensland fever, but the disease now is called Q fever no matter where it originates. The earliest American case, a laboratory infection, was described as "Nine Mile fever" because the ticks, from which Davis, Cox and Parker isolated the causative rickettsia, were collected at a place in Montana called Nine Mile. In outbreaks of the disease in Greece and Italy during World War II it became known as "Balkan grippe," but as this was shown to be Q fever it is hoped this term will be discontinued. Why not begin to call it Coxiella burnetii fever? This has the advantage of stressing its important clinical feature, fever, and distinguishes it from

other fevers by stating its etiology This name is in keeping with usage in various other diseases, such as pneumococcus pneumonia, streptococcus pneumonia meningococcus meningitis, etc

Historical

In 1933 there appeared in Brisbane, Australia mainly among workers in a large slaughterhouse a new infectious disease which was christened Q fever or Queensland fever[3] The malady has continued to appear in that region, not only among workers in the slaughterhouse but also among farmers and dairymen It was first described adequately in 1937 by Derrick[1] (for references to papers prior to 1941 see Dyer and Topping[1]) and the etiological agent, a rickettsia, was isolated in 1938 by Burnet and Freeman In the latter year Davis Cox and Parker isolated a filter passing organism in Montana from the tick *Dermacentor andersoni* During 1938 a laboratory worker, who spent four days in the Montana laboratory, returned to his regular post at the National Institute of Health at Washington D C and after an incubation period of 11 to 15 days developed a fever, which was shown to be due to a rickettsia closely allied to if not identical with the organism isolated by Burnet from Australian patients In 1940 Hornibrook and Nelson[31] described an outbreak of pneumonitis among workers at the National Institute of Health, and Bengston demonstrated by immunological methods that the causal organism was identical with Burnet's rickettsia obtained from the Brisbane cases In 1941 Hessdorfer and Duffalo reported an isolated case of human infection with the same organism in Montana In the winter of 1943-1944 Caminopetros[17] of the Greek Pasteur Institute isolated from the blood of a patient suffering from an acute respiratory disease in Athens a rickettsia which was identified by the U S Commission on Acute Respiratory Diseases as a strain of *R burnetii* In July and August 1945 sixteen employees working in the laboratory of the Commission at Fort Bragg North Carolina, came down with an acute febrile illness with extensive pulmonary involvement which was shown both by direct culture and immunological reactions to be Q fever due to *R burnetii* of the Balkan grippe strain[5] In 1946 Robbins and his associates[6] described epidemics of Q fever in American troops in the Mediterranean area which occurred during 1944 1945 and in the latter year the disease appeared at Camp Patrick Henry Virginia among troops recently repatriated from Grottaglie,

Italy where the disease *undoubtedly was acquired*[1,20] *In 1946* Cheney and Geib[3] showed that the disease was present in Panama and in March 1946 an explosive outbreak of Q fever closely paralleling the original epidemic in Brisbane Australia appeared at Amarillo Texas among stockhandlers and slaughterhouse workers[8] In 1947 Young[9] reported its occurrence in Artesia Los Angeles County California and since then cases have been reported from Los Angeles Ventura Santa Barbara and Orange Counties[11,12,22,23,24], *until by 1950 it has been estimated that* 50 000 cases of Q fever had occurred there in Southern California Cases now have been reported also from Northern California[11] from Chicago[7], from Washington D C[3] from Arizona from New England[13] from Montana from New York State[2] from France[6] from Spain[17] from Switzerland[14,56] from Great Britain[16,49] from Germany[15] from Austria[19,24] from Roumania[20] from Israel[1] from Panama[5] from *Morocco*[15], *from the Near East*[21] and *from various countries of the* Mediterranean area[18] and so without going into greater detail it is obvious that Q fever already has become a disease of wide geographic distribution and that *it should be considered as a possible diagnosis in any* group of patients developing a febrile disease of the nature described later in the section Symptomatology It is to be expected that cases eventually will be reported from most of the states of the U S A from Canada and many other countries of the world

Definition

Q fever is a rickettsial infection due to *Coxiella burnetii* (*Rickettsia burnetii*) or closely allied strains *It is characterized by* fever of sudden onset and variable duration with persistent headache and sometimes chills and sweats and by pulmonary lesions with minimal physical signs but obvious x ray indications of consolidation

Epidemiology

The outstanding fact about the epidemiology is that transmission probably occurs in several different ways Two groups of patients may be recognized (1) those spontaneously infected (2) those infected in laboratories in which investigation of the causative rickettsia is under progress Analogy with other rickettsial diseases would suggest that

other fevers by stating its etiology This name is in keeping with usage in various other diseases such as pneumococcus pneumonia, streptococcus pneumonia meningococcus meningitis, etc

Historical

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One point is crystal clear and that is that this is one of the diseases in which as in undulant fever laboratory infection[11, 2, 24, 3, 15] must be guarded against by a meticulous protective technique

Recent epidemiological studies have indicated that cows and calves[4, 11, 7, 8] are the important links in the causation of Q fever in man and that sheep and goats[11] also may play a role in its epidemiology but *one of less importance than cows and calves* *Grouping these together* as cattle cattle can be said to be the route of infection into man of *Coxiella burnetii* with resultant Q fever This relation has been studied best in California Bell Beck and Huebner[3] have summarized their studies in a paper published on March 25 1950 in the Journal of the American Medical Association They have investigated immunologically using the complement fixation test and by questioning 1, 000 persons in Los Angeles and have concluded that there the most frequent and by far the most important sources of human infection were local dairy cows their very young calves and some of their raw products particularly raw milk and hides and that the persons most apt to have been infected were those who had used raw milk in their households those whose residence had been located near a dairy or livestock yard those who had worked in industries handling live or recently killed local dairy cows and young calves e g *employees in dairies* in meat packing plants and fat rendering plants and employees handling the raw products of such animals e g employees of creameries and hide plants These studies indicate that man may contract Q fever either by ingestion by contact or by air transmission and that in some outbreaks cows infested with *Coxiella burnetii* dominantly are the responsible agent Since sheep and goats as in Northern California by serological studies have been found to be infected extensively with these coxiella sheep in 37 9 per cent *and goats in 43 6 per cent when linked with human cases and in about* 3 per cent as observed in slaughterhouses they may be expected to be productive of outbreaks of Q fever in man

Another mode of transmission of Q fever also has been demonstrated namely patient to patient infection[1] with the probability of human carriers i e individuals recovered from Q fever and even well individuals with no history of an antecedent attack Q fever also has been contracted by laundry workers coming in contact with clothing and bed linen used by individuals sick with Q fever and by contacts during post mortem examination of a patient dead of Q fever

It is evident that epidemiologically Q fever has unusually numerous

insect vectors are likely to play a role in some outbreaks but a history of tick bites in victims of the disease is rarely obtainable although it is known that in Australia the bandicoot may carry infected ticks usually strains of *Hemaphysalis humerosa* (Warburton) In Spain *Hyalomma savignyi* collected from sheep have been shown to contain *Coxiella burnetii*[17] In the United States it has been shown that the common dog tick, *Rhipicephalus sanguineus*, is capable of acting as a host to the rickettsia and that several varieties of tick found in the country can harbor it[30] These latter are *Ornithodorus turicata, Dermacentor andersoni, Otobius megnini* (a spinose ear tick), *Dermacentor occidentalis* (a dog tick) and *Amblyomma americanum* (the lone star tick)[2] The last named has been shown by Parker and Kohles to harbor the rickettsia in Eastern Texas It seems probable that this rickettsia will be found in other varieties of ticks and possibly in other insects some or all widely distributed in the world

In some of the tick hosts the rickettsiae are found in enormous numbers in the feces so that the possibility of transmission of the disease through crushing of the tick and soiling of the skin as occurs in trench fever and Rocky Mountain fever must be considered In the Amarillo epidemic most of the patients had been in close contact with cattle[5], but tick infestation in the cattle was rare and examination of rats trapped in the neighborhood showed no rickettsiae and negative agglutination reactions Furthermore a few of the victims were office employees who did not come into direct contact with cattle There was evidence that this outbreak might have been dust borne and that possibly healthy-appearing cattle might carry the rickettsiae in the urinary or intestinal tracts There was a suggestion that the Grottaglie epidemic might have been transmitted by mites

In the laboratory outbreak at Fort Bragg most of the victims were employees who worked with or were exposed almost daily to infected animals or eggs inoculated with the Balkan grippe strain The fact that workers who developed the disease, did not wear masks while those who wore double masks escaped suggested air-borne infection in the outbreak as did the fact that some cases developed in a room adjoining the egg room in individuals who did not come in contact with inoculated eggs infected tissues or contaminated glassware In the outbreak at the National Institute of Health there was evidence of transmission from person to person perhaps by droplet infection There is also the possibility of transmission through unobserved breaks in the skin particularly in slaughterhouse workers and perhaps also in laboratory workers

Pathology

The gross pathology of Q fever shows no distinctive organic changes. There is *acute spleen tumor and cloudy swelling of the liver* and kidneys such as might be found in any severe acute infection. Microscopically the spleen shows deposition of hyaline material and *debris in the follicles with diffuse congestion and dilatation of the sinusoids;* there is infiltration of the pulp by moderate numbers of large lymphoid and plasma cells and a few neutrophiles. The kidneys show *swelling of the glomeruli and tubular epithelium, some irregular infiltration* with lymphocytes and casts in the collecting tubules. The liver may show congestion of the centers of the lobules and some cellular necrosis. *The most characteristic changes are in the lungs which show* areas of congestion and consolidation. The consolidated areas are rich in fibrin, and the cells composing the exudate are erythrocytes and lymphocytes *for the most part with some plasma cells and large mono*nuclear cells. Allen and Spitz state that some interstitial pneumonitis may be present and that this is indistinguishable from that which may occur in scrub typhus, rheumatic fever and toxoplasmosis. *Pleural* effusions from which the specific rickettsia sometimes may be isolated occur in some patients.

Symptomatology

In the original article on Q fever, published in 1943, one of the present authors (Blumer) suggested a division into general and pneu*monic types. In the light of more extensive knowledge of the disease* the validity of this classification is questioned. After all, x rays of the chest were not made in the original Queensland epidemic, although Derrick did note rales in a few of the patients. No doubt roentgenograms would have shown pulmonary changes in the Brisbane patients, for the disparity between the paucity of the physical signs and the obvious x ray changes is a striking characteristic of the disease. It should be noted that on account of the great variability in different epidemics the following is a composite picture.

The incubation period is believed to vary usually between 14 and 26 days, although in the laboratory outbreak at Fort Bragg one patient had an incubation period of approximately 11 days.

The method of onset has varied in different outbreaks. In some the

methods of propagation from a large variety of already demonstrated sources including man ticks mites cows calves sheep goats, camels and nageln with the probability of others being found as the field of investigation widens It is no wonder that Q fever has been found a frequent infection among individuals with such possible contacts Immunological studies[11-15] in Los Angeles have shown that many individuals with a history of having had a mild fever especially ones with some respiratory tract involvement, had had unrecognized Q fever So it is obvious that Q fever must occur far more frequently than previously had been thought to be the case

Etiology

The causal agent of Q fever *Coxiella burnetii* (also described as *Rickettsia diaporica* and *Rickettsia burnetii*) is a pleomorphic rod which unlike many rickettsiae is small enough to pass through N and W Berkefeld filters The organism is a minute gram negative pleomorphic rod averaging 1 micron long and 0 3 microns in width Many of the rods are short and plump and simulate micrococci Long forms several microns in length are found sometimes It stains red by the Machiavello method, blue with Castenada s stain and purple in Giemsa preparations In impression smears most of the rickettsiae are extracellular but in animals usually they are intracellular and may when massed, show in tissues as inclusion bodies twenty to thirty microns in diameter In ticks the rickettsiae are present in the feces in enormous numbers a fact which may be of importance in the epidemiology of the infection *Rickettsia burnetii* will not grow on ordinary culture media but can be cultivated readily on embryonated hens' eggs inoculated by the yolk sac method from the sixth to the eighth day or by the allantoic or intravenous routes in twelve day embryos The eggs after inoculation, are incubated at 35 degrees Centigrade for a week at the end of which time the embryos usually are moribund or dead and the rickettsiae are present in large numbers especially in the yolk sac preparations This ease of growth facilitates the preparation of suspensions or rickettsiae for diagnostic agglutination tests and for the production of vaccines Guinea pigs and mice are the test animals inoculated most commonly the so called dilute brown Agouti mice being the latest type successfully used

often are injected The tongue is dry There may be a general lymph adenopathy, which is not very pronounced the enlarged nodes being discrete and firm Jaundice has been described in some patients In some epidemics a palpable spleen was present in a quarter of the patients, in others palpable spleens were not present In recent epidemics skin rashes have been absent although Derrick described a fine papular rash in about one third of the Brisbane patients

The physical signs of lung involvement often are slight although in the laboratory outbreak at Fort Bragg they were described as striking Localized areas of fine crepitant or moist rales are the most common findings Occasionally coarse rales are heard Rarely diminished reso nance minor changes in breath and voice sounds and a decrease in fremitus are noted In rare patients a friction rub or signs of pleural effusion have been noted Abdominal distention is said to be absent Cyanosis is unusual

The common laboratory examinations are not helpful in diagnosis The urine shows febrile albuminuria and cylindruria As a rule the red cell count and the hemoglobin percentage are within normal limits or there may be mild anemia The leucocyte count tends to be normal in the early stages of the disease and the neutrophiles are apt to average 70 per cent but moderate leucopenia often occurs During convales cence there may be a slight leucocytosis and in some patients there is a decrease in neutrophiles and an increase in eosinophiles The blood sedimentation rate usually is elevated during the course of the disease and continues to be higher than normal during the convalescent period and sometimes after this Blood cultures when taken have been nega tive The Kahn reaction has been negative and no heterophile agglu tinins have been noted in patients on whom this test was made Sputum examinations show no preponderant bacterial type

The pulmonary radiograms show either single or multiple lobe involvement in a large percentage of the patients The lower lobes are most likely to be affected but signs of consolidation may show in any lobe The earliest shadows usually are peripheral often circular in shape and with a ground glass density The hilar regions commonly are free from involvement The infiltrations are as a rule focal and small often not more than one centimeter in diameter and as a rule are ill defined They may persist from a few days to several weeks often for a consid erable time after the febrile period has ended Individual films may simulate primary atypical pneumonia tuberculosis or bacterial pneu monia In dubious cases serial films may be necessary for diagnosis

disease appeared insidiously in the majority of patients, in others a sudden onset has been more common It seems likely that these differences perhaps are due to variations in the intensity of the infection and that the more severe attacks are likely to begin suddenly

At onset headache has been the outstanding complaint in many of the patients It is described as severe and persistent, usually frontal and occipital in location aggravated by cough and not infrequently accompanied by pain and stiffness of the neck This last symptom may be severe enough to suggest meningism, although lumbar punctures in such patients are reported as negative With the headache are the usual accompaniments of an acute infection, malaise weakness (at times amounting to prostration) chilliness in some patients more or less severe sweats backache and general aches and pains in the muscles Frank rigors occasionally occur but are not common In some patients drenching sweats are described also insomnia

Of the respiratory symptoms cough is the most frequent, usually dry but at times productive and patients may complain of soreness in the chest or even acute pain which at times is associated with localized pleurisy In some outbreaks symptoms of upper air-passage infection are present, sneezing or sore throat with nasal stuffiness Gastrointestinal disorders such as anorexia, nausea and constipation are not uncommon and occasionally diarrhea occurs Some of the more severely infected patients may be drowsy or even stuporous

The fever varies both in intensity and in duration It is usually of the continuous type and the daily range varies with the severity of the infection Sometimes there are twice daily drops in temperature With swings in fever rigors and drenching sweats often occur In mild cases the temperature may never go above 100°F or may even be normal while in the severest ones temperatures as high as 105 4°F have been recorded The duration of the fever in mild cases may be only 3 days while in severe ones it may continue for 24 days or even longer The temperature usually falls by crisis but in some patients a fall by lysis occurs As a rule the respiratory rate is not significantly abnormal and the pulse tends to be relatively slow except in patients who are severely infected

Prostration often is marked and delirium is frequent Average duration is a week but cases occur with fever lasting for a month Complications are rare but pleurisy may be demonstrated Skin rash, as in other rickettsial diseases is extremely infrequent

The physical signs are not particularly significant The conjunctivae

disease The clinical findings in the early stages do not differ from those of many infectious diseases and until specific laboratory tests become positive such diseases as influenza the enteric fevers brucellosis sand fly fever dengue and also other infections of the rickettsial group can not be positively ruled out After pulmonary lesions have been detected a problem still remains for these cannot be differentiated by physical diagnosis and the x ray from the findings accompanying the so called atypical pneumonias which have been observed so frequently in recent years

The chief aids to differential diagnosis are agglutination and complement fixation tests for those of the infections for which they are available blood and stool cultures radiograms of the lungs and careful clinical scrutiny especially for evidence of skin eruptions such as may occur in the typhoid paratyphoid group many rickettsial infections and dengue

Prognosis

The prognosis of Q fever usually is very favorable although the severity of the disease varies widely in different outbreaks Fatalities are very infrequent usually in old individuals Among the 55 patients in the Amarillo epidemic there were deaths in the endemic at Camp Patrick Henry there were 1 8 cases with no deaths

Treatment and Prevention

The treatment of Q fever has been so far purely symptomatic and should include good nursing in sanitary surroundings an adequate diet with free fluid intake and the use of general sedatives for the severe headache and muscular aches and pains which so commonly accompany the infection Aspirin combinations of codeine and aspirin and even opiates may be required to control adequately the pains Cough seldom is severe but some patients may require sedative cough mixtures Para amino benzoic acid which has been used with definite benefit in patients with Rocky Mountain spotted fever may be tried out in Q fever if the antibiotics are ineffective Aureomycin[1 41 4 57] has been used effectively in Q fever and its use is advised in dosage as described for nonbacterial pneumonia (see Chapt XXVII B in Vol IV of Oxford

Complications and Sequelae

In some patients convalescence is unusually slow, and relapses are noted occasionally In the Fort Bragg laboratory outbreak 25 per cent of the 16 patients had relapses, one about the sixty sixth day, and in him symptoms were still present 4 months after onset In a few patients pleurisy with effusion occurs, and this necessarily prolongs the illness Alopecia, such as may occur after typhus and typhoid has been noted occasionally A few patients have developed corneal ulcers A late arthritis has been observed, also rare cases of orchitis and epididymitis George Burke[1] reports that occasionally endocardial involvement may occur in patients running a chronic course

Diagnosis

Although the symptoms and physical signs of Q fever are not distinctive its association with certain industries notably the cattle industry, may be suggestive particularly in outbreaks involving numbers of people The main reliance in diagnosis must be placed on positive agglutination or complement fixation tests made with the patient's serum and suspensions of *Rickettsia burnetii* Agglutinins usually develop in the second or third week of illness and maximum titers may not be reached before the fifth or sixth weeks Occasionally agglutinins may be detected as early as the tenth day whereas in mild cases they may not appear until the fifth week (Fort Bragg epidemic) The titer of agglutination tends to drop after two months A titer of less than 4 has no diagnostic significance, whereas in positive cases titers of above 60 are common and occasionally those above 500 are encountered Complement fixation tests usually agree with agglutination tests and like them, reach their height during convalescence Intraperitoneal inoculation of guinea pigs or mice with the blood centrifugalized urine or pleural effusion of patients may result in the recovery of the organism from the spleens of animals that develop fever or may furnish serological evidence of the type of rickettsia involved through reactions in the blood of inoculated animals At times the rickettsiae can be visualized after direct inoculation of egg embryos with human material

Differential diagnosis of Q fever in the early stages may be quite impossible unless associated phenomena such as laboratory infection or limitation to a particular occupational group point directly to the

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Medicine) Good results have been reported too from treatment with chloramphenicol (chloromycetin)[13, 14], so if aureomycin does not seem effective then chloramphenicol (chloromycetin) should be given in dosage as recommended for typhoid fever (see Vol IV Chapt XX of Oxford Medicine)

Prophylactic immunization is theoretically possible and should be considered when definite geographical foci of infection are present

Prevention should consist of avoidance of contacts with known cases and with cows calves sheep and goats and their products known to be infected including especially not using raw milk Unfortunately ordinary pasteurization does not always kill coxiella in the milk, so milk from cows known to be infected should be boiled

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CHAPTER XVI

TYPHUS FEVER AND BRILL'S DISEASE

By ANDREW YEOMANS

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INTRODUCTION

Synonyms Epidemic European old world historic jail fever camp fever war fever Fleckfieber (German) tabardillo (Spanish) typhoesantematico (Italian)

Typhus fever is a disease characterized by high fever skin rash and pathological involvement of blood vessels throughout the body The etiological agent is an intracellular organism *Rickettsia prowazeki* There are a number of diseases caused by rickettsias which are pathogenic for man These diseases

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March 1 1951

in Russia steadily increased It has been conservatively estimated that between 1917 and 1921 there were more than 25 million cases in Russia with over 3 million deaths[4]

While for some years there was a decline in typhus on the European continent following World War I epidemiological reports[4] have shown that between 1930 and 1935 local epidemics occurred in Russia Poland Roumania and Yugoslavia involving thousands of cases with a considerable mortality Likewise outbreaks occurred in North Africa and in Egypt

The reporting of typhus fever from Russia was halted in 1937 and from the beginning to the end of World War II there were for obvious reasons few data available concerning the extent of typhus fever in Germany but the recent increase in typhus literature from Germany makes it clear that this disease was of considerable military importance on the Eastern Front Severe epidemics of typhus probably were existent in Poland Yugoslavia Roumania and Western Russia Typhus fever was present in Spain in 1941 and 1942 and in Egypt in 1943[4] in epidemic proportions Two thousand cases per month were seen in one Cairo hospital alone during the spring and early summer of that year

Typhus fever was found in Naples and its suburbs after the Allied occupation of that city in the fall of 1943 The institution of prompt measures of control was responsible for limiting the epidemic to about 1 900 cases[4] As the Allied Armies fought their way into Germany in 1945 louse borne typhus was discovered in numerous localities in Germany and surrounding liberated countries After the cessation of hostilities in May 1945 a typhus survey of Germany Austria and parts of Czechoslovakia revealed a wide dissemination of this disease which prevailed in the larger towns and cities and in the smaller communities as well

Louse borne typhus fever probably was introduced first into South America and Mexico by the Spanish during their early conquests[3] Since that time the disease has been seen in the colder regions of South America Central America and Mexico

In 1836 Gerhard[7] described an outbreak of typhus fever which occurred in Philadelphia The observations made by Gerhard and his associate Pennock on the epidemiology clinical course and post mortem findings in this epidemic served clearly to differentiate typhus from typhoid fever Since 1836 numerous small outbreaks of louse borne tyhpus have been described in the United States The cases have been confined almost exclusively to port cities on the Atlantic Seaboard but occasionally have been seen in the far West[3] The last big epidemic occurred in New York City in 1892 presumably arising from a shipload of Russian immigrants[3]

Typhus fever was introduced into Canada several times during the 19th century by the large numbers of Irish immigrating to Canada The disease is no longer existent there

may be divided into four groups These we may call the typhus group the Rocky Mountain spotted fever group tsutsugamushi disease (scrub typhus) and Q fever At present these four groups of diseases appear distinct from one another not only on immunological grounds but also from the point of view of their trans mission Typhus is transmitted by lice or fleas Rocky Mountain spotted fever in the United States and related diseases in other parts of the world by ticks and tsutsugamushi disease by mites Q fever probably is transmitted by ticks For lack of definitive data trench fever and Bullis fever, now believed to be caused by rickettsia are considered to be outside these four groups

This chapter is limited to a discussion of the typhus group of fevers louse borne typhus murine typhus and Brill s disease These diseases are so similar in their clinical pictures that no differentiation can be made between them in the individual case except by epidemiological considerations specific serological tests and differences in the behavior of the rickettsias of louse borne and murine typhus in experimental animals Louse borne typhus fever is by far the most serious of the three diseases of the typhus group A clinical description of louse borne typhus differs only from a clinical description of murine typhus and Brill s disease in the overall severity of the course of illness the frequency of complica tions and the case fatality rate The reader should keep these facts in mind since in this chapter emphasis will be placed on a comprehensive discussion of the clinical course of louse borne typhus

Historical

Although there are accounts of epidemics dating back to the ancient Greeks, the descriptions given of them are so general that it is difficult if not impossible to distinguish a particular disease especially typhus fever Typhus however probably has been present in various populations in the world for hundreds of years

Fracastorius (1546)[1] is generally credited with the first clinical description of typhus fever He remarks that this disease was present in epidemic form in Italy in the early 16th century However an account of a fever occurring in a monas tery near Salerno in 1083 is believed by Zinsser[2] and Hirsch[3] to have been typhus fever In 1489 typhus is presumed to have killed thousands of soldiers in the siege of Granada in Spain In the 17th, 18th and 19th centuries typhus returned many times in epidemic proportions in Europe and in the British Isles particu larly during the 30 Years War (1619–1648) the French Revolution the Napoleonic Wars and the Crimean War The first country to be afflicted with a typhus epidemic in World War I was Serbia from the autumn of 1914 to the spring of 1915 it was estimated that over 150 000 persons died Other countries on the Eastern Front were similarly afflicted with typhus From 1914 to 1921 typhus

Brill's Disease

In 1910 Brill[14] described a group of cases seen in New York City which clinically resembled European louse borne typhus fever. At that time he hesitated to term these cases typhus but described their illness as an acute infectious disease of unknown origin. In 1911 this investigator believed that the disease was a form of modified European typhus fever[16]. In 1912 Anderson and Goldberger[17] reported the transfer of virus from patients with Brill's disease to rhesus monkeys and observed that monkeys recovering from an attack of the disease were immune from further infection by the same virus and showed cross immunity to Mexican typhus. Since Brill's first description of the disease many cases have been seen in New York and Boston. Zinsser and Castaneda[18] were able to obtain a strain of rickettsias from a patient with Brill's disease which resembled the European louse borne virus. Zinsser[19] on the basis of epidemiological and immunological data postulated that Brill's disease is a recrudescence of European typhus. Almost all cases occur in Jews of European origin who have come from endemic centers of louse borne typhus. The disease is not associated with lousiness and the mortality is almost nil.

Etiology

The causative agent of typhus is a comparatively recent discovery. In 1909 Nicolle, Comte and Conseil[0] first demonstrated that blood from typhus patients was infectious for monkeys and they succeeded in passing the virus from monkey to monkey by means of lice. Ricketts and Wilder (1910)[1] confirmed the work of Nicolle and his collaborators and showed that human body lice could transmit typhus to a monkey either by feeding infectious lice on the animal or by introducing the louse feces and louse intestines into the skin.

Ricketts and Wilder[2] in the same year described minute poorly staining bipolar organisms seen in the peripheral blood of typhus patients from the 7th to the 12th day of disease. These investigators not claiming that the organism described was the etiological agent suggested that further search be made for a bacterium as the cause of typhus. Previously they had shown that the virus was not passed through a Berkefeld filter.

In 1913 Hegler and von Prowazek[23] described the experimental transmission of typhus virus from patients to guinea pigs and a monkey by intracardial and intraperitoneal inoculation of infective blood. Von Prowazek made smears from numerous infected lice and in one preparation he found small cocci like bodies.

Two important papers by da Rocha Lima published in 1916[4] emphasized the close association of typhus with rickettsias. In these papers he described the transfer of virus through guinea pigs to monkeys and back to guinea pigs and

Murine Typhus Fever

Although epidemic louse borne typhus has not occurred in the United States for many years, a considerable number of typhus cases are seen here every year The greatest number of these cases occur in the Southern states, particularly in those bordering on the Atlantic coast and the Gulf of Mexico During the past 5 years the majority of typhus cases have occurred in Texas Georgia, Alabama Louisiana and Florida

Recent facts concerning the epidemiology of typhus in the United States have been an important contribution to the knowledge of the epidemiology of typhus throughout the world In 1926 Maxcy[10], reporting on epidemiological studies of typhus in the southeastern United States, drew attention to the fact that the greatest number of cases were seen among people employed in groceries, food stores and restaurants and that there was a notable absence of the disease among unskilled or unemployed workers

Also there was an important lack of contact cases and a very low familial attack rate in contrast to louse borne typhus Further, the disease was not associated with lousiness From these and other data Maxcy postulated that the reservoir of the disease was in rats or mice and transmitted to man through the bite of a parasitic blood sucking arthropod

The interest in searching for a rodent reservoir and the arthropod vector of this disease led to the discovery by Dyer, Rumreich and Badger[11] of a typhus virus in fleas collected from wild rats at a typhus focus in Baltimore In the same year Dyer, Cedar Lillie, Rumreich and Badger[1] reported the experimental transmission of typhus virus by the rat flea Mooser Castaneda and Zinsser[13] isolated a typhus virus from the brains of rats trapped in Mexico City It was shown by Cedar Dyer Rumreich and Badger[14] that the virus of endemic typhus could remain virulent in the rat flea for as long as 5 weeks and that the probable mode of transmission of the virus to the host of the flea was through contamination of skin abrasions by flea feces

These important discoveries of the reservoir and vector of endemic typhus in the United States have been confirmed by investigators in many other parts of the world Endemic or murine typhus is the most widely disseminated of all the typhus fevers It can occur in the same locality where louse borne typhus is present

On clinical grounds alone it is impossible to distinguish murine typhus from louse borne typhus in the individual case The decision as to which form of disease exists rests on epidemiological data on the isolation of rickettsias and on certain serological tests later to be discussed Murine typhus is a less severe disease than louse borne typhus The mortality rate in the United States is below 5 per cent The control of murine typhus depends upon the control of rats

In Giemsa preparations *Rickettsia prowazeki* assumes a faintly bluish tinge By Machiavello technique[7] they appear red against a bluish background

The position of the *Rickettsiaceae* in the general classification of micro-organisms is at present uncertain The pathogenic rickettsias for man appear to be closely associated with the viruses because they multiply only inside living cells On the other hand their inability to pass through filters of a certain size and their visibility under usual microscopic methods seem on these grounds to separate them from the usual viruses The rickettsias which are found in cases of louse borne typhus and Brill s disease are called *Rickettsia prowazeki* var *prowazeki* to distinguish them from the rickettsias isolated from patients with murine typhus which are called *Rickettsia prowazeki* var *mooseri* While there is evidence to show that rickettsias are highly toxic to certain animals[8] it has not been established that a toxin exists apart from the living rickettsial bodies themselves When rapidly frozen in a bath composed of solid carbon dioxide and alcohol and kept at a temperature of − 76 C rickettsias retain their virulence for months

Pathology

Except for skin lesions there are no findings at the post mortem table which can be termed typical of typhus At the time of death the majority of cases

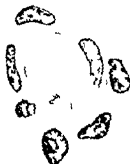


Fig 2 Rickettsia prowazeki in endothelial cells of the skin Mexican typhus Human case Courtesy of Palfrey and Wolbach

exhibit a rash The early skin lesions which have not yet become hemorrhagic disappear rapidly following death In a few instances however I have observed

showed that the inoculation of infective material in these animals produced an immunity to later infective doses of virus He described the development of rickettsias in cells of the louse gut and found that, while these organisms developed in lice fed on typhus patients, they were found but rarely in normal lice fed on convalescent or non typhus patients He concluded that these organisms were the long sought etiological agent of typhus fever but was uncertain as to their position in the classification of bacteria In honor of two famous investigators in typhus research he named these organisms *Rickettsia prowazeki*

In 19 o the controlled investigations of Wolbach Todd and Palfrey [5] showed that intracellular rickettsias were found in lice nourished on typhus patients and that these infected lice when injected into guinea pigs produced pathological lesions of typhus, in which rickettsias were found and were identical with lesions seen in human typhus These fundamental investigations, since confirmed in many parts of the world proved that *Rickettsia prowazeki* is the cause of louse borne typhus fever

Rickettsias belong to a group of microorganisms classified tentatively at the moment under the family *Rickettsiaceae*[6] In size they are somewhat smaller



Fig 1 Smear preparation gut of louse infected with *Rickettsia prowazeki* 1 500 diameters Courtesy of Palfrey and Wolbach

than most bacteria and usually they show considerable variation in shape Rickettsias appear as minute cocci diplococci or cocco bacilli (Fig 1) Rapidly growing rickettsias may exhibit filamentous forms Rickettsias are nonmotile and multiply only within living cells They stain poorly with the usual dyes

most commonly in the skin brain and spinal cord heart liver kidneys and spleen The invasion of the endothelial cells of the blood vessels by rickettsias results in the formation of mural thrombi or occluding thrombi Proliferation of the capillary endothelium may occur A perivascular infiltration about such lesions in the capillaries consisting of lymphocytes plasma cells and large mononuclear cells has been termed a nodule Aside from these nodules a diffuse perivascular infiltration may be seen in some organs notably the heart and kidneys The classical rash of typhus is evidence of lesions in the skin

The pathological changes which occur in louse borne typhus fever have been described fully by Wolbach Todd and Palfrey[5] and the reader is referred to their monograph for a detailed account of the histopathology of this disease

Transmission of Epidemic Typhus Fever

The spread of epidemic typhus fever depends upon the presence of human body lice *Pediculus humanus* var *corporis* The head louse *Pediculus humanus* var *capitis* is not considered an important vector of the disease Body lice live in the clothing worn next to the skin The female louse lays its eggs in the seams of the cloth The favorite localities are the regions of the neck band axilla and waistline The eggs of the louse hatch in about 10 days When a louse feeds on the skin of a typhus patient the rickettsias circulating in the patient s blood are drawn into the intestinal tract of the louse The rickettsias invade the epithelial cells of the midgut and multiply in enormous numbers Eventually these cells rupture and the rickettsias are expelled in the louse feces The invasion of the cells lining the intestinal tract of the louse by rickettsias causes the death of the louse usually in fewer than 10 days Rickettsias are not transmitted from the female louse to the eggs Infected lice do not regurgitate the virus in feeding The rickettsias from louse feces may penetrate the skin during the act of scratching louse bites or crushing lice between the fingers It is believed now that the deposition of infected louse feces on the mucous membranes of the conjunctival or respiratory tract is an important mode of transmission of the virus While blood from a typhus patient is infectious during the febrile course of illness the urine feces and secretions from the respiratory tract are not The reservoir of the virus of louse borne typhus during interepidemic periods is at present unknown

Clinical Course

Incubation Period

Ordinarily the period from the time of infection to the onset of the clinical disease is 12 to 14 days It is likely that with massive infective doses this interval

patients dying in the second week of the disease in whom the skin lesions were so scanty that one would be unable to say at post mortem that the patient had a typhus rash in life. Symmetrical gangrene of the extremities is a striking finding in a few cases. Areas of skin necrosis may be seen often over points of pressure such as the sacral area. One may find extensive hemorrhage into the soft tissues underlying such areas. Extensive hemorrhages may be found in the tissues in other parts of the body such as the muscles of the abdominal wall. The gross



FIG 3 Early typhus lesion in a human artery of the skin. Courtesy of Palfrey and Wolbach

findings of bronchopneumonia, a brownish colored flabby myocardium with yellowish streaks and spots and an enlarged soft spleen are found frequently in typhus as in other acute infectious diseases. The kidneys often display pinhead sized circular, dark red hemorrhagic spots on their surfaces and petechial hemorrhages in the pelves and occasionally the ureters. Frequently the cortical tissue of the adrenal glands contains areas of hemorrhage which often appear to replace entirely the cortical substance. The intestinal tract in typhus usually is without significant gross findings.

The microscopic lesions in typhus are unique and widespread throughout the body. The histopathology consists of lesions of the small blood vessels (Fig 2 and 3). Almost every organ of the body may be involved but lesions are seen

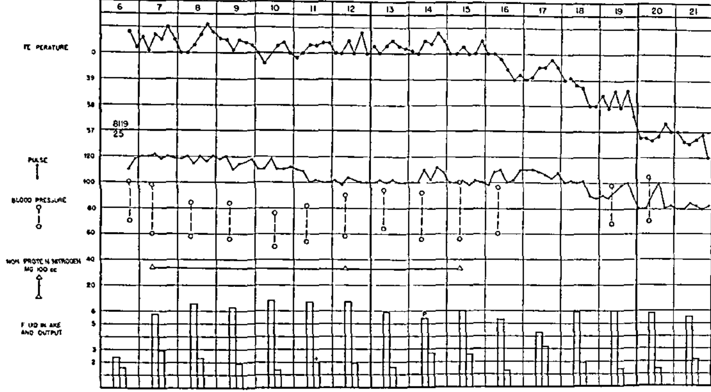


Fig 4 The clinical chart of a 25 year-old man hospitalized on the 6th day of disease Stupor developed during the first hospital week with incontinence of feces by the 12th day Due to skin pigmentation the rash was not definite before the 11th day Despite a low blood pressure there was no evidence of peripheral circulatory failure or nitrogen retention Rectal temperatures are in degrees Centigrade The P over the fluid intake column indicates parenteral administration of fluid The + s over the fluid output column indicate incontinence of urine From the Cairo Unit of the U S of A Typhus Commission

may be shortened considerably [9] During the incubation period there are no demonstrable evidences of illness

First Week of Disease Unvaccinated Patients

Symptoms — The clinical onset of typhus usually is described as sudden with few prodromal symptoms Occasionally however one may observe patients with symptoms of mild headache and malaise which are present for one or two days before the beginning of severe symptoms In my experience the period of mild symptoms is accompanied always by fever The majority of patients are first aware of the sudden onset of malaise with shivering sensations or a true rigor followed in a few moments or hours by headache which may be mild at first but quickly grows intense The headache may be generalized but in most cases is frontal and pulsating in type The headache is continuous and remains in most cases until defervescence and in some cases, into the convalescent period Headache is the cardinal symptom of typhus It is severe and not relieved easily by analgesics even in large doses Patients may experience mild recurrent chills during the first two or three days of the disease, but they are rarely observed after the third day

Severe discomfort in various parts of the body begins early in the first week of the disease Movement of the back knees or shoulders on turning in bed may be exceedingly painful Much discomfort is noted on pressure over the thigh or calf muscles The myalgia and arthralgia usually remain prominent symptoms throughout the illness

A non productive cough is seen commonly in the first week of disease with occasional expectoration of a tenacious sputum The early onset of cough and sputum is characteristic and emphasizes the early pulmonary involvement in typhus Vomiting is present sometimes in the first 3 or 4 days of illness and may be explained by the frequent anorexia found at that time but it is not often seen after the 4th day except in patients who develop azotemia Constipation is far more common than diarrhea in the first week of illness

Tinnitus aurium may appear as early as the third day of disease and usually is bilateral Patients may complain also of deafness early in the disease but this symptom as well as tinnitus aurium, appears most often in the second week

Fever — Fever is found almost universally with the appearance of symptoms, and in rare cases it is noted before the patient complains of feeling ill The temperature rises to 103° or 104° F in 48 to 72 hours and persists for from 12 to 18 days in uncomplicated cases In cases unaccompanied by bacterial infection defervescence usually occurs by lysis over a period of three to five days It is unusual to observe a febrile course of less than 12 days in hospitalized cases of

The Rash — A distinctive feature of typhus and the most important clinical diagnostic sign of the disease is the skin rash This may be apparent as early as the 3rd day or as late as the 10th day In my experience the rash does not appear



FIG 6 A 25 year-old man on the th day of disease The rash was profuse with multiple petechiae involving the hair follicles on the legs This patient developed oliguria azotemia a large area of skin necrosis over the sacrum and otitis media Recovery was complete From the Cairo Unit of the U S of A Typhus Commission U S Army Signal Corps Photo #2920

before the 3rd day of disease but may be seen in o per cent of patients on the 3rd day 60 per cent of patients on the 5th day and in over 80 per cent of patients on the 6th day of disease

Before the rash is seen many experienced observers have remarked upon a peculiar marbled appearance of the skin This is considered to be the immediate percursor of the typhus rash This marbling phenomenon has been called

typhus over 16 years of age In a group of 36 male patients studied recently the average course of illness was 18 5 days[5] In the presence of secondary infections such as pneumonia parotitis, otitis and abscesses the high sustained fever of typhus gives way to a remittent lower fever curve between the 14th to the 18th day of illness A swinging type of fever curve then may persist for varying periods of time depending upon the severity and type of complication present The fever curve of a typhus patient who is receiving no antipyretic drugs is high,

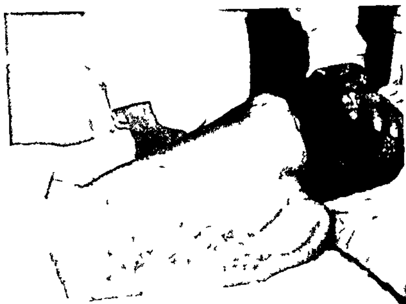


FIG 5 A 35 year-old man on the 10th day of disease This patient developed oliguria and skin necrosis on the right shoulder and glans penis multiple skin abscesses and erysipelas Recovery was complete From the Cairo Unit of the U S of A Typhus Commission U S Army Signal Corps Photo #2920

ordinarily running between 104° and 105° F in extreme cases with rare remissions of more than half a degree during the 24 hour period (Fig 4) Indeed, there are few acute infectious diseases encountered in which the fever is sustained at such a high level for such a long time as in louse borne typhus Persistent rectal temperatures of 104° F or higher for 10 or more days are not uncommon However, during the period of defervescence there may be considerable remission in the morning temperatures Although febrile relapses which are attributed to a recrudescence of the disease have been described in typhus[30] I have not observed them except in patients who have received para aminobenzoic acid[5]

The Rash — A distinctive feature of typhus and the most important clinical diagnostic sign of the disease is the skin rash This may be apparent as early as the 3rd day or as late as the 10th day In my experience the rash does not appear



Fig 6 A 25 year-old man on the 7th day of disease The rash was purpura fuse with multiple petechiae involving the hair follicles on the legs This patient developed oliguria azotemia a large area of skin necrosis over the sacrum and otitis media Recovery was complete From the Cairo Unit of the U S of A Typhus Commission U S Army Signal Corps Photo #2920

before the 3rd day of disease but may be seen in 20 per cent of patients on the 3rd day 60 per cent of patients on the 5th day and in over 80 per cent of patients on the 6th day of disease

Before the rash is seen many experienced observers have remarked upon a peculiar marbled appearance of the skin This is considered to be the immediate percursor of the typhus rash This marbling phenomenon has been called

subcuticular mottling The skin seems translucent, as if one were looking through it and could discern a faint plexus of bluish vessels beneath its surface Subcuticular mottling is observed most often about the shoulders and upper chest It is not present always, but when noted, it is an interesting aspect of the disease

The rash consists of macules and papules which can be felt by light stroking with the index finger These lesions are light pink at first with indefinite borders



FIG 7 A 35 year-old man with a profuse hemorrhagic rash This patient developed azotemia skin abscesses and otitis media The photograph on the left was taken on the 10th day of disease that on the right was taken on the 24th day and shows the degree of emaciation which commonly develops during typhus The rash is still visible From the Cairo Unit of the U S of A Typhus Commission U S Army Signal Corps Photo #2412 2923

They may vary in size from 2 to 4 mm in diameter but sometimes are larger In the early stages the lesions fade completely on pressure In 24 to 48 hours these lesions which are papular often lose their elevation and together with macular lesions become dark red and are circumscribed They no longer fade on pressure but are 'fixed The larger lesions frequently are indurated they never become pustular

The lesions first appear on the lateral aspect of the chest wall over the upper chest the upper back the flanks and the inner surface of the upper arms As the rash increases, more lesions make their appearance in these areas and lesions are seen on the lower arms particularly the flexor surfaces on the lower back,

buttocks and thighs (Figs 5 6 and 7) An extensive typhus rash covers the entire body from the neck to the dorsum of the hands and feet The palms of the hands (Fig 8) and soles of the feet become involved rarely even in severe cases It is important to note that the rash in typhus begins on the trunk and spreads peripherally in contrast to the rash of spotted fever which is seen first on the



Fig 8 Skin lesions on the palm of the hand on the 10th day of disease From the Cairo Unit of the U S of A Typhus Commission U S Army Signal Corps Photo #1898

extremities The rash is almost never seen on the face or on the forehead in typhus an important distinguishing feature from the rash of spotted fever or fievre boutonneuse As the disease progresses the macules become dark red or bluish red Then they turn brown and gradually fade out

During the course of severe typhus macular lesions may coalesce to form large hemorrhagic areas several centimeters in diameter Petechiae may be seen together with macular lesions They occur most often on the extremities and may

be so numerous that each individual hair follicle is involved (Fig 6) Patients with profuse rashes develop petechiae on the conjunctival mucous membrane and on the buccal mucosa or the soft palate In desperately ill or fatal cases it is not uncommon to observe the successive appearance of new lesions over a period of several days Consequently, in these instances one may observe pink lesions interspersed among dark red or bluish ones

The skin of patients on whom the rash is developing rapidly or is profuse shows a generalized livid erythema In a few patients the skin may display an icteric tint It is hot and dry The peripheral veins are full, the radial pulses bounding As the rash develops the skin of the face, forehead and neck assumes a dusky cyanotic hue The face becomes puffy, the eyelids edematous The temporal arteries are engorged with visible pulsations The conjunctival vessels become enlarged particularly the vessels running from the canthus to the limbus corneae giving the conjunctivae a look of intense injection As the rash on the body disappears the conjunctival injection decreases and the face returns to its normal color

The duration of the rash is variable Macules may still be visible as late as the fourth week after disease onset or they may be gone before the temperature has reached normal levels As a rule the rash has faded out by the end of the third week In a few patients the disappearance of the rash is accompanied by the development of a generalized sudamina

On the whole there is a close correlation between the extent and profuseness of the rash and the severity of the clinical course of the disease Most patients dying from typhus and not from secondary complicating conditions show an increasing rash until death Daily observation of the rash is therefore important from the prognostic point of view In rare instances however, one may observe a typhus patient dying in the acute disease in whom the rash was at all times scanty or fading at the time of death In this category, of course belong those light skinned individuals in whom the rash is never seen for certain, yet the patient succumbs to proven louse borne typhus I recently observed such a case At autopsy material from the bone marrow obtained by sternal puncture was inoculated into fertile hens eggs A strain of rickettsia was recovered which displayed reciprocal cross immunity with the Breinl strain of typhus fever[31]

Summary — From what has been said of the clinical course of typhus during the first week of the disease the most distinctive features mentioned have been the headache and the rash Several additional findings although not diagnostic, are of interest The *heart rate* usually increases during the first week to between 110 and 130 beats per minute in the moderately or severely ill patient In others the rate may remain below 100 beats per minute until the second week The heart sounds are strong and the heart action forceful A gallop rhythm is heard rarely during the first week of illness The *systolic blood pressure* may begin to

fall toward the end of the first week of the disease In typhus the characteristic fall in peripheral blood pressure is closely correlated with the appearance of the exanthem The degree of hypotension varies considerably in individual patients Although the blood pressure may decline during the first week of illness it very rarely reaches a level of 90 mm Hg or below before the 8th day *Pulmonary signs may be noted toward the end of the first week of the disease These usually* consist of coarse rhonchi heard over both lung fields particularly over the lower half of each lung field Occasionally coarse râles are present over the lower lobes Rarely I have noted consonating râles during the first week *The sputum* is tenacious but rarely blood streaked *The spleen* commonly is enlarged in typhus and becomes palpable in over 50 per cent of cases by the 6th day of disease It is not usually tender to palpation unless much enlarged *Hepatomegaly* is observed rarely at any time during the course of typhus The appearance of *delirium or stupor* depends largely upon the severity of the clinical course of typhus Although at times they may be observed as early as the fourth day they are not seen ordinarily before the 6th day of disease even in patients who die in the second week *Nuchal rigidity* is a rare phenomenon during the course of typhus fever and is almost never seen during the first week of illness The *tendon reflexes* particularly the patellar and achilles occasionally may become hyperactive or depressed In a few patients *constriction of the pupils* manifests itself during the course of typhus This phenomenon usually is coincidental with the efflorescence of the rash and may therefore occur in the first week of illness

The Second and Third Week of Disease Unvaccinated Patients

Symptoms and Signs — The critical period of illness begins in the second week of the disease and may extend through the first 3 days of the third week The moderately or severely ill patient shows increasing prostration during the second week He complains bitterly of generalized body discomfort Because of weakness and stupor often he is unable to take nourishment except with continual nursing assistance Headache often is very intense Photophobia may be present Tinnitus may increase and subjective and objective deafness may be complete A persistent cough with difficulty in expectoration is common A muttering delirium often appears or the patient may discourse rapidly for hours with imaginary friends The speech may be slurred or scanning or the words uttered in an explosive manner Periods of apparent mental tranquillity may alternate with sudden outbursts of shouting weeping or laughing A deep stupor may follow such episodes but usually the patient can be aroused for true coma vigil is rare except in fatal cases Some patients are quite active Continuous athetoid movements of the body and extremities may persist for days and require constant restraint Urinary incontinence commonly begins in the second week and may

persist well into convalescence Incontinence of stools is a frequent finding in cases with extreme prostration and stupor My impression is that incontinence of urine and feces is due to weakness and lethargy rather than to loss of sphincter control on neurological grounds Retention of urine may appear also during the second week and require an inlying catheter for a period of days Intractible hic coughs are a frequent accompaniment of progressive azotemia

Physical examination during the second week commonly discloses a widespread and fixed rash The face is of a dusky hue the conjunctivae intensely injected Petechiae may be present on the conjunctivae or in the mouth In cases with severe dehydration the tongue is dry fissured and may have a thick brownish coat The mucous membranes of the mouth have a dull glazed appearance The tongue is tremulous and is protruded with difficulty The respirations are rapid and shallow with almost no movement of the chest wall The heart sounds may be distant and a third heart sound frequently is present at the apex giving the heart rhythm a gallop character Extensive pulmonary signs may be present consisting of percussion dulness over the lower lobes of the lungs with consonating rales and dulness over various other portions of both lung fields The abdomen may be distended and tympanitic The reflexes may become hyperactive with a well sustained bilateral ankle clonus A positive Babinski phenomenon some times is present Voluntary movements of the extremities may be uncoordinated and purposeless An arm extended passively from the shoulder may remain there until replaced on the bed In cases with azotemia (Fig 10) coarse periodic tremors of the extremities with picking of the bedclothes are common The fists may remain tightly clenched for days resulting in maceration of the skin of the palms In fatal cases large dark red areas appear over the sacrum and occasionally on the abdominal wall and extremities indicating extensive subcutaneous hemorrhages In roughly 75 per cent of patients the blood pressure falls to a level of 90 mm of Hg systolic or below by the 9th day of disease It may remain at this level for an indefinite period but ordinarily rises during defervescence In spite of the low systolic blood pressure evidences of peripheral vascular failure are seen seldom except in fatal cases a few hours before death

In patients who recover from the disease a diuresis precedes in some instances the decline in temperature by 24 to 48 hours When such diuresis occurs one may be reasonably sure that the end of the period of high fever is at hand This sign is of value in cases where the exact day of disease is unknown As I have pointed out rapid defervescence is unusual except in patients who are mildly ill Once the decline in fever has begun and provided no complications are present one may anticipate recovery The duration of delirium and stupor is variable Following a severe course of illness some patients remain disoriented well into convalescence Stupor may persist after defervescence Other evidences of severe central nervous system damage may lead one to doubt whether the patient will survive How

ever with reasonably good nursing care death from typhus during the convalescent period is almost never seen in the absence of febrile complications

Many patients complain of tinnitus aurium and may be almost totally deaf during convalescence These symptoms and signs however rarely have been seen to persist longer than 10 months following the disease except in patients who developed otitis media with perforation as a complication of their illness Usually *tinnitus and deafness have disappeared by the fourth week* *Generalized muscular* weakness with tachycardia on moderate effort may persist for several weeks or months following severe typhus but in this regard it should be said that the majority of patients even though desperately ill recover so completely that they can be found doing strenuous labor months after disease onset

Immunity Following Typhus Fever

Recovery from louse borne typhus fever ordinarily produces an immunity which lasts for years Although second attacks of typhus have been recorded from regions where the disease is endemic they are on the whole very rare In experimental animals an attack of louse borne typhus fever confers immunity against infection with the murine disease and vice versa Presumably this is true in man

Laboratory Data

Hemoglobin and Red Blood Cell Count — Practically all patients who are more than mildly ill develop an anemia during the course of the disease During the second and third week of illness the red blood cell count commonly is reduced to between 3 0 and 3 5 million cells per cubic millimeter with a corresponding reduction in hemoglobin values The anemia may persist for varying periods during convalescence but usually there is a rapid return to normal values with no specific treatment

White Blood Cell Count — A leucopenia is the common finding during the first week of the disease The white count may range from 2 000 to 7 000 cells per cubic millimeter Differential counts may show a slight increase in monocytes Eosinophils are seen seldom at any time during the acute disease When the rash is developing the white blood cell count may be increased to between 10 000 and 12 000 cells per cubic millimeter and occasionally a leucocytosis of from 15 000 to 30 000 cells per cubic millimeter may be present In such instances there is rarely an increa e in the polymorphonuclear cells

Urine — Practically all patients exhibit an albuminuria of varying degrees during the febrile course of illness In severely ill and fatal cases a heavy albuminuria may be present The specific gravity of the urine during the first week

may be high because of dehydration During the second and third weeks of the disease critically ill patients may excrete small amounts of urine of relatively low specific gravity In such cases azotemia is either present or imminent During early convalescence the specific gravity is low The urine volume may fluctuate considerably from hour to hour with no changes in fluid intake Red blood cells are seen in varying numbers in the urinary sediment Gross hematuria is rare Granular casts are often found in great numbers in cases with nitrogen retention Red blood cell casts and waxy casts are seen rarely at any time throughout the disease

Roentgenogram of the Chest — Recent pathologic studies of the lungs in typhus patients have demonstrated a type of interstitial pneumonitis which may be visible on x ray examination of the chest Frequently one observes a diffuse mottling of various portions of the lung fields at a time when physical signs of pulmonary involvement are minimal

Electrocardiographic Changes — The majority of patients show electrocardio graphic changes during the acute disease The most common abnormalities have been low voltage of the QRS complexes with low or inverted T waves and oc casionally depression of the S–T segment[30, 33] Delay in the interventricular conduction time has been described[33] but is rare In my experience electrocardio-graphic changes which may occur during the acute disease, disappear in con valescence in almost all instances

Azotemia — A rise of the blood nonprotein nitrogen is a frequent finding in typhus usually beginning early in the second week of the disease[31] In a few in stances azotemia appears associated with extreme dehydration and the excretion of a urine of high specific gravity Generally the onset of azotemia is not asso-ciated with obvious dehydration but accompanies a fall in blood pressure with a reduced output of urine, often of low specific gravity However azotemia may appear and increase steadily over a period of days with no reduction in blood pressure or urine volume A rise in the blood nonprotein nitrogen to values of 110 to 200 mgm per 100 c c can occur with eventual recovery but usually such rises signify a fatal outcome The highest value for the blood nonprotein nitrogen which I have observed was 277 mgm per 100 c c 2 days before death Recent studies have indicated that kidney damage in typhus may be a frequent compli cating condition[34] Azotemia often is associated with a reduction in renal plasma flow which in certain instances may be of importance in the production of kidney damage[35]

Serum Proteins — A reduction in the serum albumin with a rise in serum globulin occurs in over 75 per cent of typhus patients[32, 35] This phenomenon frequently appears late in the first week of illness and continues throughout the second and third weeks An inversion of the albumin globulin ratio is found often in the first week of disease Low values for serum albumin may be associated

with visible edema Total serum protein values may be reduced during the acute disease During early convalescence the serum globulin may attain values of 5 gm per 100 c c A slow return of the protein fractions to normal values occurs usually in 2 months following the disease

Serum Chlorides — Reduction of the serum chlorides below 95 m eq per liter is a common finding during typhus occurring in my experience in over 50 per cent of patients Values of 85 m eq per liter may be found as early as the 6th day of disease A reduction in serum chlorides regularly is associated with a reduction in urine chloride The serum chlorides may remain low throughout the disease but usually return to normal levels during early convalescence without the addition of salt to the diet The administration of 5–10 grams of NaCl per 24 hours results in a return of the serum chlorides to normal values before defervescence in the majority of instances and in rare cases this salt intake per 24 hours results in excessively high serum chlorides with resulting edema

Acid base Equilibrium — Abnormally high values for the CO_2 combining power of the blood have been reported in typhus patients showing reduction in serum chlorides[37] However recent studies[35] on 53 typhus patients have failed to demonstrate the presence of alkalosis even though a reduction in serum chlorides was found to be quite common The administration of sodium bicarbonate to patients with severe renal damage due to typhus may result in greatly elevated serum CO_2 content In fatal cases with severe azotemia one may observe serum CO_2 contents as low as 15 m eq per liter Nevertheless in these cases the serum pH has been found to be normal in almost every instance

The Blood Volume — Recent studies have failed to substantiate the assumption by some investigators[37] that a significant reduction in the whole blood volume takes place in severe typhus fever accompanied by hypoproteinemia or oliguria and hypotension These studies[35] performed on patients who while receiving adequate routine nursing care nevertheless developed hypotension and azotemia with or without oliguria showed that the plasma volume was almost always within the accepted normal range

A slight reduction in the whole blood volume was seen in patients studied during the second week of the disease but this reduction could be accounted for by a reduction in red cell volume alone While it is conceivable that significant reductions in plasma volume may occur in typhus patients who receive inadequate nursing care in respect to the oral intake of fluids it is apparent that severe hypotension associated with oliguria and azotemia occurs in the presence of a normal plasma volume

Nitrogen Balance — Marked loss of weight is commonly observed during the febrile course of typhus fever (Fig 7) Recent studies[35] have shown that such weight loss was accompanied by a greatly increased output of nitrogen in the urine When typhus patients were fed a daily diet of 4 000 calories containing

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Castaneda[39] and others[40, 41]. In general the test is now carried out as follows: A suspension of proteus organisms usually stained with methylene blue is mixed on a glass slide with a drop of blood from the suspect's finger or ear. In cases with appreciable proteus OX19 antibodies clumping occurs in one to three minutes. In using this test ideally one should include a positive and negative serum sample as a control. Within certain limitations this test was found to be of great value in the control of typhus epidemics in World War II when it was necessary to test rapidly large numbers of persons *in the field for suspected or recovered typhus*.

A test has been described[42] for the early diagnosis of typhus fever in which the unknown suspected typhus serum (antigen) is brought into contact with convalescent serum (antibody) in the presence of complement. With this test a positive complement fixation reaction has been obtained in 100 per cent of typhus cases as early as the first and second day of the disease. The test is uniformly negative after the 10th day. Although not yet confirmed outside of Russia, further experience with this test may prove it to be an important contribution to the early diagnosis of typhus fever.

Complement fixation Test. — The complement fixation test using rickettsias as antigen has been of great value in confirming the diagnosis of typhus fever[43 ( ), d (b), 44 ( ), d (f)]. This test has been positive in nearly all clinical cases of typhus fever studied by the United States of America Typhus Commission during World War II[35] and has been found positive in many instances when the clinical picture was doubtful but the isolation of rickettsias from the patient's blood proved the diagnosis. Although the test is of no value in the early diagnosis of the disease since it becomes positive usually in the second week, a high titer of complement fixing antibodies may be present for many months or years[44 (a)] following typhus fever. Recent studies[44 (b), 45 ( ) and (b)] have shown furthermore that by the complement fixation test usually one can distinguish between louse-borne and murine typhus except in some cases where typhus has been contracted following vaccination with the epidemic strain of rickettsias.

In such cases the titer of the complement fixation test using murine antigen may be as high as that found with the epidemic antigen. Therefore one must exercise caution in the interpretation of this test as evidence for murine or louse-borne typhus in vaccinated individuals and take into account other important data such as the epidemiological findings associated with each case, agglutination tests using both epidemic and murine rickettsias and where strain isolation is possible the antigenic behavior of the strain isolated.

In unvaccinated patients some cross fixation may occur between the epidemic and murine antigen but the titer of fixation is uniformly higher in the homologous serum. Inasmuch as the Weil-Felix agglutination reaction is positive in high titer in both epidemic and murine typhus and one cannot distinguish between the two diseases on clinical grounds alone, it is apparent that the complement fixation

over o grams of nitrogen, the weight loss in many patients was greatly reduced throughout the acute disease, and convalescence was more rapid No definite relationship was found between the severity of the disease and the total nitrogen excretion Also there was no indication that the daily intake of over 20 grams of nitrogen increased the level of the blood nonprotein nitrogen above normal values

Weil Felix Reaction — In 1915 Weil and Felix[36] found that typhus serums agglutinated a strain of proteus organisms known as the OX19 strain This phe nomenon has been used as a standard test for the diagnosis of louse borne typhus murine typhus and Brill s disease Beginning usually about the 5th to 7th day, a rising titer of agglutination of these organisms by typhus serums may be found in over 90 per cent of unvaccinated patients Serums of patients suffering from other diseases than typhus fever occasionally may agglutinate proteus OX19 organisms in high titer (1 640) dilution but such titers are static Therefore it is important to point out that in typhus demonstration of a rise in titer throughout the disease is of the greatest importance in evaluating this test Highest titers in typhus are found usually late in the second week less often throughout the third and fourth weeks after the onset of illness Usually the titer falls rapidly during the 4th to 8th week after the disease onset and may be entirely negative by the 12th week There has been considerable discussion as to what constitutes a diagnostic rise in the titer of the Weil Felix reaction Felix[37] has stressed the fact that there may be two types of reaction to this test in typhus patients One type is characterized by an early rise in titer to later very high levels which may persist for a considerable period following recovery The other type shows a late rise to low levels during the disease with early disappearance during convalescence There may be no significant rise in cases which terminate fatally Other sero logical studies[35] have shown likewise that in some cases of clear cut clinical typhus the Weil Felix reaction may show either no rise in titer or a rise to only 1 160 throughout the entire disease while in others the agglutination titer may reach levels of over 1 10 000

The different techniques employed by various laboratories in performing the test the different types of response to the production of OX19 agglutinins pointed out by Felix and the time during the course of the disease at which serum samples are taken must all be considered in determining what constitutes a significant rise in titer in the individual case This is particularly true when low titers are en countered during the disease and in early convalescence In such cases it remains for the clinician to evaluate the results of this test in the light of the clinical find ings and other serological tests A demonstrable rise in titer to 1 320 or above, on the other hand can be considered in almost every instance serological evidence of a typhus infection In recent years the agglutination of proteus OX19 organ isms by typhus serum has been used as a rapid field test for typhus This test, described by Holt Harris and Grubbs[38] has undergone various modifications by

isolation is therefore of importance in patients whose clinical course is atypical or in whom the serological tests discussed previously are equivocal The isolation of rickettsias from patients with typhus is a complicated procedure involving the services of a well equipped laboratory and specially trained personnel Although rickettsias may be recovered from the patient s blood late in the febrile course the optimum time is before the 10th day of disease Usual methods of strain isolation involve preliminary steps such as the injection of the patient s blood directly into laboratory animals usually guinea pigs or into fertile hen s eggs or the feeding of a colony of uninfected lice on the skin of a patient for period of 7 to 10 days and the transmission of the virus from these lice to laboratory animals The failure to demonstrate multiplication in a cell free media is one of the criteria for establishing the rickettsial nature of organisms isolated from a typhus patient The methods devised by Cox[63] for the cultivation of rickettsias obtained either directly from the patient or from laboratory animals injected with the patient s blood have simplified the techniques for studying rickettsial strains Repeated passage of a particular strain of rickettsias in fertile hens eggs affords abundant material for the study of the biological behavior of the isolated strain and for comparison with other rickettsial strains The demonstration of reciprocal cross immunity in animals between a strain of rickettsias isolated from a patient and known strains of either murine or classical louse borne typhus is the final proof of the diagnosis of typhus fever

Diagnosis

In persons under 16 years of age the diagnosis of typhus often is difficult and frequently impossible without the aid of laboratory tests The disease is mild in the majority of cases The fever course may be short with but a moderate elevation in temperature Headache may be minimal or absent and the rash may never appear or be so faint as to be easily overlooked In children typhus often is diagnosed as influenza in situations where adult members of the same household have been ill with recognizable typhus and where the presence of typhus in the children should have been strongly suspected In patients of any age group the diagnosis cannot be made with certainty before the appearance of the characteristic rash During an epidemic however the presence of louse infestation, a history of contact with typhus and the signs and symptoms described earlier allow one to make a presumptive diagnosis of typhus with reasonable assurance in patients seen early in the disease

The Weil Felix and complement fixation tests described in the section on laboratory data are rarely helpful during the first week of the disease The rickettsial agglutination test likewise is of doubtful value before the 6th day of disease After the first week of illness however these three tests are of definite

test using both epidemic and murine antigen, is of value in differentiating these two diseases In cases of Brill's disease the complement fixation test gives a higher titer with epic m c antigen than with murine antigen[44(a)]

Although there is now some evidence[46] to show that a considerable number of vaccinated typhus patients who contract the disease, have very low titers of proteus OX19 with no demonstrable rising curve of agglutination, the complement fixation rises to as high titers in adequately vaccinated persons, who contract the disease as n unvaccinated persons[45(b)] It is important to determine the complement fixation titer in all suspected cases of typhus since as mentioned above the OX19 agglutination titer may be so low as to be equivocal

Two recent studies[47 48] have shown that a rise in complement fixation may be seen following booster doses of typhus vaccine One of these studies[47] showed a rise to as high as 1 128 dilution in one case with a tendency for the titer to decline to the pre "booster level in 8 weeks' time In the other study[48] a booster' dose of vaccine produced complement fixing antibodies in titers of 1 512 dilution or higher lasting for at least a month in several instances The facts obtained from these studies must be borne in mind in the evaluation of the complement fixation test in persons suspected of having typhus who recently have received a "booster" dose of vaccine As in the interpretation of the Weil Felix test the demonstration of a rising titer of complement fixing antibodies is of greatest importance In a serological study[49] of individuals vaccinated against typhus fever, who were suffering from other acute febrile diseases it has been shown that as a rule no rise in complement fixation occurs except in the rare case and then the rise is minimal It seems probable therefore that the slight rise seen occasionally in vaccinated patients suffering from acute febrile diseases other than typhus should cause little confusion in diagnosis

Rickettsial Agglutination Test — Recent studies [50 51 5] with purified rickettsial suspensions of epidemic and murine rickettsias obtained from yolk sac cultures have shown that a differentiation can be made between epidemic and murine typhus Agglutination of the rickettsias in higher titer by homologous serums is the basis for this differentiation The titer of agglutination rises during typhus but in mo t instances falls to low levels (1 160 or less) in 3 to 10 months after the disease

Plotz and Snyder[50] state that occasionally high titers of rickettsial agglutination with epid mic and murine typhus antigens may be seen in serums from cases of Rocky Mountain spotted fever This fact should therefore be kept in mind in interpreting the rickettsial agglutination test as a diagnosis for typhus fever

Isolation of Strains — The recovery of a strain of rickettsias from the blood of a suspected case of typhus and the demonstration that such a strain has the antigenic characteristics of rickettsias of the louse borne or murine type of virus sometimes is of great value in confirming a diagnosis of typhus fever Strain

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value in confirming the diagnosis of typhus and are of special aid in cases where the rash is questionable or absent With respect to all three tests it is of greatest importance to obtain serum samples as early as possible in the disease and at frequent intervals thereafter at least once weekly, in order that a rising titer of agglutination or complement fixation may be demonstrable A single serum sample taken during or following the disease is often of little value

Differential Diagnosis Unvaccinated Typhus

A number of infectious diseases must be considered in the differential diagnosis of louse borne typhus fever Among the most important are the following

Smallpox — Smallpox and typhus epidemics frequently may occur together The onset of the two diseases is similar Once the lesions of smallpox appear, however the diagnosis usually is clear since the fever rapidly declines, and the lesions are dissimilar in appearance and distribution from those of typhus The differential diagnosis between a case of vaccinated typhus and a case of vaccinated smallpox may be very difficult except by serological tests

Relapsing Fever (Louse Borne) — Epidemics of relapsing fever may occur frequently with epidemic typhus fever The onset of the two diseases is not only similar, but the fever curve and symptoms of relapsing fever during the first week of the disease may closely simulate that of typhus When present the rash of relapsing fever may constitute a source of confusion Fortunately, blood films disclose the presence of spirochetes in the relapsing fever patient

Malaria — Malaria must be considered in all regions where malaria is seen with typhus fever and particularly when the patient may have had suppressive treatment Blood films are of the greatest importance in excluding malaria from the differential diagnosis

Typhoid Fever — This disease for centuries has been confused with typhus fever As a rule, the onset of typhus is more sudden and the patient is more prostrated in the first week of the disease than in typhoid There are almost no remissions of the fever in typhus and a heart rate below 110 beats per minute is seen rarely after the first week of illness The exanthem in the two diseases is not easily confused when the typhus rash is distributed over the body However in the typhus patient with scanty lesions located only on the trunk the differential diagnosis may be very difficult and rest entirely on blood or urine cultures and serological reactions

Meningitis — The absence of nuchal rigidity and positive Kernig sign and lack of stupor during the first week in most typhus cases are of aid in the differential diagnosis of typhus and spinal meningitis In typhus fever the spinal fluid is clear usually not under pressure contains few cells and the dynamics are normal A leucocytosis in typhus is rare except during efflorescence of the rash

Measles — The rash of measles may be confused with the rash of typhus but the pronounced symptoms and signs of coryza and the presence of Koplik spots in measles are useful distinguishing features in most instances

Murine Typhus — Although louse borne typhus is a much more severe disease than murine typhus it is not possible to distinguish the two diseases clinically in the individual case *The rash is similar and the Weil Felix reaction is positive* in both diseases However the intraperitoneal inoculation of murine rickettsias often produces an inflammation of the tunica vaginalis[54, 55] of male guinea pigs which is seldom produced by rickettsias of louse borne typhus Also murine rickettsias are agglutinated in higher titer by homologous serums than epidemic rickettsias In unvaccinated patients a higher titer of complement fixation is obtained in the homologous serum than in the heterologous serum when the test is run with both epidemic and murine antigen These findings together with epidemiological considerations are useful in distinguishing between murine and louse borne typhus in man

Rocky Mountain Spotted Fever — The difference in the appearance and distribution of the rash of spotted fever and typhus has been referred to in the section on the rash of typhus The rash of spotted fever is more hemorrhagic in character *resulting in frequent skin necroses A distinguishing feature between typhus and* spotted fever from the pathological viewpoint is that the rickettsias of spotted fever invade the cell nuclei and that the medial coat of the blood vessels is involved Dyer[56] has stressed the fact that the Weil Felix reaction gives no aid in the differentiation between typhus and spotted fever for although the agglutination of the proteus OX_2 strain by spotted fever serums occurs more frequently than in typhus the OX19 agglutination by spotted fever serum is at the same time usually higher than the OX_2 agglutination The complement fixation test using the spotted fever rickettsias as antigen is of value in the serological diagnosis of this disease

Prognosis and Mortality Unvaccinated Typhus

The mortality of louse borne typhus in the white race is high and the death rate increases with the age of the patient The mortality figures in Table I are in agreement with figures obtained in other epidemics of the disease It is important to note that the patients listed in this table were natives of a country where louse borne typhus fever has been endemic for many years Nevertheless the case fatality rate was high particularly in the older age group

Although death from naturally acquired typhus as opposed to laboratory infections has been reported in the first week of the disease in my experience it has never been seen before the 8th day in cases where the onset of disease could

value in confirming the diagnosis of typhus and are of special aid in cases where the rash is questionable or absent With respect to all three tests it is of greatest importance to obtain serum samples as early as possible in the disease and at frequent intervals thereafter, at least once weekly, in order that a rising titer of agglutination or complement fixation may be demonstrable A single serum sample taken during or following the disease is often of little value

Differential Diagnosis Unvaccinated Typhus

A number of infectious diseases must be considered in the differential diagnosis of louse borne typhus fever Among the most important are the following

Smallpox — Smallpox and typhus epidemics frequently may occur together The onset of the two diseases is similar Once the lesions of smallpox appear, however the diagnosis usually is clear since the fever rapidly declines and the lesions are dissimilar in appearance and distribution from those of typhus The differential diagnosis between a case of vaccinated typhus and a case of vaccinated smallpox may be very difficult except by serological tests

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perience such cases die within 24 to 48 hours A *bacterial pneumonia* which develops in the second week of the disease carries a high mortality The most helpful single sign in predicting the severity of the clinical course and the eventual outcome in typhus is the presence and degree of *azotemia* or *nitrogen retention* in the blood Patients may appear seriously ill with delirium or profound stupor a profuse rash lowered blood pressure and incontinence but if daily observation of the blood nonprotein nitrogen shows no elevation above 45 or 50 mgm per 100 c c it may be expected that practically all such patients will survive the disease Azotemia is routinely present in cases which are comatose or show evidences of peripheral vascular failure generalized cyanosis or convulsions However in the absence of these signs a progressive increase in nitrogen retention is observed sometimes and in the majority of such cases the prognosis is poor A further discussion of azotemia will be in the next section

Complications and Complicating Conditions

A frequent and often fatal complication which occurs in typhus is a *bacterial pneumonia* This is almost invariably seen at post mortem in fatal cases is usually confluent in type and involves the greater portion of the lower lobes Its onset is seen most often in the second week but it may develop also in the early third week and occasionally in early convalescence Increasing respiratory rate purulent sputum and leucocytosis are the common signs associated with this condition

A migratory type of pneumonitis may be seen in a number of patients who are extremely ill (Fig 9) Roentgenograms will show infiltration in various parts of the lung fields as the disease progresses which may last for a considerable period of time in convalescence It is not clear yet whether this type of pneumonitis is primarily of bacterial or rickettsial origin

The development of *furuncles* and *necrosis* of the skin over pressure points is a common complication in patients where adequate nursing care is not available The frequency with which infections of the skin are seen during typhus stress the necessity for special nursing care to patients who are more than moderately ill

Parotitis is encountered in about 10 per cent of typhus patients under usual conditions of hospitalization seen in epidemic areas This is a serious complication of the disease As pointed out under the section on treatment its incidence can be reduced to almost zero by frequent administration of fluids by mouth and the avoidance of a solid or semisolid diet throughout the period of acute illness

Otitis media is a frequent complication following parotitis It may be seen also in the absence of parotitis

Symmetrical gangrene of the extremities particularly the feet is observed with variable frequency in different countries In my experience it is uniformly

TABLE I

Typhus Fever in the Cairo Fever Hospital *
January 1 1943 to September 1 1944

Ages	Males			Females		
	Cases	Deaths	Mortality per cent	Cases	Deaths	Mortality per cent
16–20	124	1 0	9 6	689	60	8 7
21–25	13(3	58	15	586	61	10 4
26–30	088	25	25 5	540	74	13 7
31–35	598	184	30 8	377	,1	18 8
26–40	422	142	33 6	232	59	25 4
41–48	264	124	47 0	135	44	32 6

Table taken from paper by R S Ecke and Associates The effect of Cox type vaccine in louse borne typhus fever Am Jour Trop Med 1945 XXV 447

be definitely determined When death occurs in cases where adequate nursing is available in the majority of instances it occurs between the 10th and 14th day of disease Since it is obvious that untreated complications may cause fatalities in typhus the quality of nursing care determines to a great extent how late death may occur after the onset of the disease When good nursing care was available, I have observed no deaths from typhus or its complications after the 18th day of the clinical disease Under such circumstances the patient who survives the first two and one half weeks of typhus fever has an excellent chance for recovery Sudden death during the acute stages of the disease may occur in patients who are not considered to be desperately ill In my experience however this type of death is seen in less than 10 per cent of fatal cases The great majority of patients exhibit certain symptoms and signs which should be stressed since they are of importance in the prognosis of the disease *Coma* during the acute disease is an ominous sign and carries a mortality of nearly 100 per cent *Convulsions* are not common in typhus but when they do occur are of serious prognostic significance I have observed but one case of typhus with convulsions which recovered *Peripheral circulatory failure* in typhus carries a poor prognosis The development of bluish cold extremities a feeble pulse and a systolic blood pressure below 60 mm of Hg all signify that death is imminent in 100 per cent of cases In such cases restoration of the blood pressure by infusions of plasma or albumin to normal levels merely prolongs life for a few hours The development of *generalized cyanosis* in the absence of severe hypotension and evidences of peripheral vascular collapse often will respond dramatically to oxygen therapy however in my ex

The development of *azotemia* (Fig 10) as a serious complicating condition of typhus has been mentioned briefly in the section on Prognosis and Mortality and now receives additional comment

The presence of glomerular nephritis in patients dying from louse borne typhus has been reported as rare by some[5] and frequent by others[47, 48] Despite

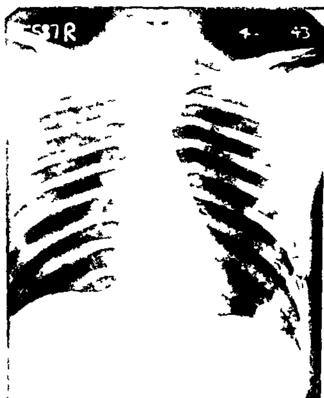


Fig 9 (*b*) Roentgenogram of same patient taken on 23rd day after onset of typhus

divergent opinions concerning the pathological findings in the kidneys of typhus patients there is now considerable evidence[34, 35] to indicate that kidney damage is a common occurrence in severe louse borne typhus fever Whether this damage is based primarily on rickettsial lesions in that organ is due to the effects of rickettsial toxic products or in some cases is due to a reduction in blood flow with renal ischemia is not yet certain One or all of these factors may play a part. However the severity of the clinical course of louse borne typhus is directly pro-

followed by death Whether such gangrene is the result of thrombosis of large vessels due to rickettsial lesions or to a neurogenic factor is, as yet, unsettled In my opinion patients who are continually chilled while sick run a greater chance of developing this complication than those who are kept warm



Fig 9 (a)

Fig 9 Chest roentgenograms of a 19 year old man taken on the 15th 23rd and 30th day after onset of typhus as shown in Figs 9(a) 9(b) and 9(c) The patient developed signs of a diffuse bronchitis with remittant fever and leucocytosis Physical examination was negative during a follow up period of 12 months From the Cairo Unit of the U S of A Typhus Commission

Jaundice is seen rarely during the actual disease or in convalescence In my experience its incidence is less than one per cent Death occurs in about half the cases which develop jaundice The cause of jaundice in typhus has not been explained adequately

Treatment

General Measures

The discovery of potent antibiotics for the treatment of rickettsial diseases makes it unlikely that in the future physicians will be forced to contend with the severe clinical course and complications of typhus

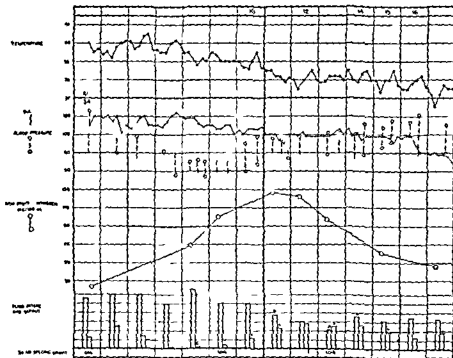


Fig 10 The clinical chart of a 34 year-old man hospitalized on the 4th day of illness The rash appeared on the 5th day and increased in intensity throughout the first hospital week accompanied by petechiae in the conjunctival and buccal mucosa Muscular twitching was seen on the 9th day The fall in blood pressure was associated with oliguria isosthenuria and azotemia Peripheral circulatory failure was not present Recovery was complete The C over the fluid output column signifies that urine was obtained by catheter only Other symbols as in Figure 4 From the Cairo Unit of the U.S of A Typhus Commission

fever as it has been known in the past Nevertheless, it is possible that under certain conditions cases late in the clinical course of the disease may be encountered or appropriate antibiotics may not be available

portionate to evidence of disturbances in kidney function The development of nitrogen retention or oliguria with low urine specific gravity are signs that point invariably to a severe course of typhus Likewise progressive nitrogen retention over a period of several days with no oliguria is an ominous sign Patients show progressive nitrogen retention for several days before death in practically all



Fig 9 (c) Roentgenogram of same patient taken on 70th day after onset of typhus

instances the important exceptions being patients who succumb to a complicating pneumonia late in the third week In the latter group of patients severe azotemia may have been present earlier in the course of illness but at the time of death the blood nonprotein nitrogen may be normal or only slightly elevated

Follow up studies of patients who developed evidences of kidney damage during the course of typhus show no residual impairment of renal function except rarely and in such cases the existence of previous renal disease has not been excluded

the application of talcum powder to the back buttocks and crotch the use of air cushions whenever possible and the hourly turning of stuporous patients from side to side In typhus fever oral temperatures are likely to be misleading Rectal temperatures are preferable With rectal temperatures of over 104°F (40°C) towels or sheets dipped in ice water and wrapped around the patient have been employed successfully in reducing fever The routine use of antipyretic drugs for reducing fever is not recommended The marked fluctuations in temperature, which may occur appear to exhaust many patients Sweating increases the loss of body water and is to be avoided

Relief from headache is afforded by an ice cap In cases with intense headache codeine in doses of 30 mgm (gr ½) subcutaneously at three hour intervals sometimes is of value Likewise codeine may be given in the dosage just mentioned for the relief of persistent cough Severe active delirium sometimes will respond to oral administration of chloral hydrate in large doses The intravenous administration of paraldehyde has been used with success in some cases It should be given slowly with caution The barbiturates have proved of doubtful value in most instances and actually have appeared harmful in some Their action is most unpredictable in this disease Their use is not advocated There is doubt whether morphine should be used in the control of delirium On occasion it has been used with no obvious deleterious effects and with benefit in sudden bouts of uncontrollable delirium but in a disease which produces severe damage to the brain and central nervous system the use of morphine may be hazardous Although the withdrawal of spinal fluid has been reported effective in relief of intense headache or in lessening uncontrollable delirium such a procedure has been of doubtful value in my experience In most typhus patients the spinal fluid pressure is not elevated except when they are very active In such cases it is conceivable that the withdrawal of spinal fluid may afford relief from headache but from personal observation I am not yet convinced that this is true

Many European physicians have recommended and routinely use strophanthin ouabain cardiazol and digitalis in typhus Since extensive cardiac lesions are found regularly in all fatal cases of typhus one may assume that there is considerable involvement of the myocardium in moderately or critically ill patients who recover from the disease However in the absence of clear cut signs and symptoms of congestive heart failure and in the absence of abnormalities of rhythm which respond to the administration of digitalis there is no justification for the use of

Therefore at this time emphasis on the importance of good nursing care and knowledge of an adequate nursing regimen is not misplaced The conditions under which epidemic typhus fever exists, the lack of food, medicines physicians and nurses, force the clinician to reduce routine nursing care to a minimum The recommended outline of care to be described will be found impossible in many instances, but when followed, this regimen has proved of great value in the treatment of this disease

Bed rest is of course essential during the febrile period and is recommended for the first two weeks of convalescence in the uncomplicated case In cases showing residua of severe nervous system damage during the first two or three weeks following the acute disease it has been found important to get such patients up from bed into a chair and to encourage the use of their limbs through simple muscle exercises or by walking with support These patients are liable to bed sores, if left in bed until activity is resumed voluntarily Such a program of active convalescent treatment often will be found to increase the appetite and in other ways be of marked psychological value to the patient

During the period of fever fluid intake should be regulated to produce an output of urine of 1,500 to 2,000 c c per 24 hours It is advantageous to administer fluids at frequent intervals throughout the 24 hours to prevent excessive dryness of the mouth and throat A satisfactory schedule is to give fluids at two hourly intervals beginning at 6 00 a m through 10 00 p m and again at 2 00 a m Subcutaneous or intravenous administration of fluids should be used in patients too ill to swallow The use of a stomach tube may be of value

The diet should be of high caloric value, 3 000 to 4 000 calories in adults preferably high in protein and vitamins In patients, who are severely ill a liquid diet may reduce significantly the need for frequent mouth care and the incidence of parotitis A sodium chloride intake of between 5 and 10 gm per 24 hours is desirable except in patients with oliguria or edema Every attempt should be made to record the 24-hour output of urine of every typhus patient and particularly of those who are severely ill Patients with retention or incontinence of urine should be put on continuous bladder drainage The blood pressure should be measured at least once every 24 hours throughout the febrile period of the disease In critically ill patients a two hourly recording of the systolic blood pressure is of importance Routine care should include thorough cleansing of the mouth at least once daily for stuporous patients at three hour intervals

Skin care should consist of daily bed baths of tepid water and soap,

the application of talcum powder to the back buttocks and crotch the use of air cushions whenever possible and the hourly turning of stuporous patients from side to side In typhus fever oral temperatures are likely to be misleading Rectal temperatures are preferable With rectal temperatures of over 104°F (40 C) towels or sheets dipped in ice water and wrapped around the patient have been employed successfully in reducing fever The routine use of antipyretic drugs for reducing fever is not recommended The marked fluctuations in temperature which may occur appear to exhaust many patients Sweating increases the loss of body water and is to be avoided

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digitalis or drugs with a similar action on the heart Congestive heart failure is seen rarely in typhus patients who recover later Rhythm abnormalities likewise are encountered rarely When one considers the pathological changes produced by the rickettsial invasion of blood vessels throughout the body, it is clear why death from typhus is accompanied most often by increasing skin lesions and evidences of a profound toxemia I believe with Woodward and Bland[3] that in such cases the degree of cardiac damage does not appear out of proportion to damage occurring in other parts of the body Although I have used digitalis and strophanthin in a small number of patients who exhibited signs and symptoms of cardiac failure immediately before death, there was no indication that these drugs were of value

It is important to deal promptly with complicating bacterial infections which may be present by appropriate antibiotic therapy There is some evidence[59, 60] to show that in animals, at least, sulfonamides may be harmful in typhus Oxygen has been found to lessen the generalized cyanosis which sometimes occurs in very severe typhus, but its use has not been in my experience a life saving measure

Certain laboratory procedures have been found of considerable value in the care of typhus patients A determination of the hemoglobin and red blood cell count once weekly is of importance in following the severity of anemia which uniformly appears during the acute disease Frequent urine examinations with particular attention directed to the specific gravity and sediment are of value in following the renal status of the patient The blood nonprotein nitrogen or blood urea nitrogen should be determined as early as possible in the clinical course of the disease In patients who are severely ill who show a sudden fall in blood pressure over a period of hours or in whom a diminution in urine output occurs which is not related to the fluid intake, the blood nonprotein or urea nitrogen should be determined daily A determination of the serum protein values and the serum albumin, particularly during the second and third week of disease indicates the severity of the hypoproteinemia and hypoalbuminemia

In the absence of hypoalbuminemia the parenteral administration of dextrose and saline solutions has been without harm and has constituted a life-saving measure in patients who were not able to take fluids by mouth However the use of these solutions is contraindicated in patients with low serum albumin or in patients with oliguria because of the probability of resulting formation of edema which is of serious consequence Typhus patients with edema or hypoalbuminemia may benefit

from the intravenous administration of human serum albumin plasma or whole blood Such benefit may be seen particularly in severely ill patients whose systolic blood pressure falls in the space of a few hours to 80 mm Hg or below with a rapid diminution in urine output In these patients the low level of the systolic blood pressure may not be suspected since often there are none of the usual signs of peripheral circulatory failure in evidence (Fig 10) Nevertheless this association of low peripheral systolic blood pressure with urinary suppression must be regarded as a serious sign The invariable occurrence of nitrogen retention follows In addition a further rapid decline in blood pressure may ensue with evidence of peripheral circulatory failure The continuous administration of plasma or albumin before the onset of peripheral circulatory failure in such cases may aid in supporting the blood pressure through a most critical period of the disease with eventual recovery

Serum Therapy, Chemotherapy and Antibiotic Therapy

The treatment of typhus with various types of immune serum has been used extensively in the past[61] Hyperimmune horse serum was used in North Africa[62] and in Ethiopia[63] with apparent beneficial results During World War II German investigators reported the beneficial use of convalescent whole blood transfusions[64, 65] and convalescent serum[66, 67] However, a review of the literature on the treatment of typhus with human convalescent serum or whole blood does not indicate that this form of specific therapy was of much value

The use of hyperimmune antityphus rabbit serum, first described by Kurotchkin van der Scheer and Wyckoff[68], has been of therapeutic effect in experimental typhus[31, 69] A trial[9] of this serum in patients with epidemic typhus was carried out on a small number of cases with gratifying results when given in the first 72 hours of the disease The large doses of this serum necessary for therapeutic effect and the time consuming method of administration precluded its wide use during recent epidemics of the disease

During World War II extensive studies were carried out in a search for a chemotherapeutic agent effective in rickettsial infections Reviews[93, 94] of these studies have appeared recently It may be stated briefly that sulfonamides and closely related compounds atabrin and an antimalarial compound called sontoquin parasulfamidobenzamidine

methylene blue (methyl thionine hydrochloride) and "nitroacridine 3582" were given clinical trials which were either inconclusive or frankly disappointing

In 194 1944 para aminobenzoic acid (PABA) was shown to exert a beneficial effect in experimental rickettsial infections[59, 72, 90a-d] Clinical trials in 1944-1945 showed encouraging therapeutic effects when this compound was given in the first week of illness to patients with louse-borne typhus[91] and other human rickettsial infections[9] -

In these rickettsial diseases of man the duration of fever was reduced and complications were encountered less often and were less severe The mortality appeared to be reduced in some series of patients which were studied with the use of these methods

The most favorable therapeutic effects from PABA in rickettsial infections are achieved only when the compound is given before the 7th day of illness Due to rapid absorption and excretion it must be given in rather large amounts 1 to 3 gm, every 2 hours throughout the day and night When the acid itself is used sufficient 5 per cent sodium bicarbonate solution should be given simultaneously to render the urine neutral or slightly alkaline in reaction Fifteen cubic centimeters of bicarbonate solution to 1 gm of the drug partially dissolves the drug and usually results in the formation of an alkaline urine Sodium para aminobenzoate is soluble in water Additional sodium bicarbonate solution need not be given with the sodium salt so long as the urine remains neutral or alkaline in reaction In the treatment of typhus patients it was found important to maintain a constant blood level of PABA (as free diazotizable substance measured against a standard of PABA) of 10 to 20 mgm per 100 cubic centimeters Since this compound has been found to depress the white blood cell count in rickettsial infections as well as in other diseases the white blood cell count should be done at least every other day as long as a patient receives the drug Extended reviews[91, 93] of PABA therapy in typhus have appeared recently in the literature to which reference should be made for further details in treatment

With reference to antibiotic therapy in rickettsial diseases it may be said that penicillin has been shown occasionally to produce a beneficial effect in experimental infections, but clinical trials were universally disappointing Streptomycin has not been given an extensive clinical trial probably due to absence of striking effects in experimental infections particularly tsutsugamushi disease Two more recently discovered antibiotics chloramphenicol (chloromycetin) and aureomycin have

been shown experimentally and clinically to alter profoundly the course of rickettsial infections

In 1947 chloromycetin or chloramphenicol as it is now called was reported to have antirickettsial action in chick embryos[95, 96] and in laboratory animals[97]. There followed rapidly reports of clinical trials of chloramphenicol in louse borne typhus[98, 99], scrub typhus[99b-d] and Rocky Mountain spotted fever[100]. The results of treatment of scrub typhus and Rocky Mountain spotted fever with chloramphenicol were particularly impressive. The therapeutic effect of chloramphenicol in typhus is a prompt defervescence in from 1 to 3 days the early disappearance of a rash if present a rapid return of a feeling of well being and no complicating conditions which so frequently occur in untreated patients. Reports to date indicate that the serological response to the rickettsial infections treated with this drug develops similarly to that seen in untreated patients

The present recommended dosage of chloramphenicol is an initial dose of 4 gm by mouth (60 mgm per kilogram) followed by 0.25 gm every three hours for at least 24 hours or until the temperature reaches normal levels. Occasional anorexia occurs with a single dose of 4 gm and may be avoided by division of the initial dose over a period of two to four hours

If, following the course of therapy a recrudescence of fever occurs which is interpreted as a relapse the patient can be given a second course of treatment. Experience in the treatment of scrub typhus with chloramphenicol to date indicates clearly that *R tsutsugamushi* does not become drug fast to repeated courses of either chloramphenicol or aureomycin. The recent work of Smadel and his associates has shown that prophylactic doses with chloramphenicol to volunteers exposed to scrub typhus will suppress the clinical disease until the drug is withdrawn when at a time beyond the normal incubation period typical scrub typhus develops. This responds readily to therapeutic dosages (see references 103e and 103f). Observations on the suppressive treatment of louse borne typhus with chloramphenicol or aureomycin are not available

Chloramphenicol cannot be given intramuscularly due to tissue reaction. It has been given intravenously to typhus patients. However oral administration appears to be preferable. Although the original clinical trials of chloramphenicol in human rickettsial infections were carried out using the fermentation type of drug recent evidence[101] shows that in experimental infections employing different types of

rickettsia and in clinical infection with tsutsugamushi disease synthetic chloramphenicol is as fully effective therapeutically as chloramphenicol produced by the mold *Streptomyces venezuelae N sp*

Aureomycin, an antibiotic recently derived from a strain of *Streptomyces aureofaciens*[10] has been shown to have a remarkably beneficial effect in experimental infections with Rocky Mountain spotted fever, murine typhus, scrub typhus, Q fever, rickettsial pox and epidemic typhus[10 b-e]. In clinical infections beneficial results from treatment with aureomycin of Rocky Mountain spotted fever[10 h], Q fever[10], Brill's disease[1 31] and scrub typhus[10] have been reported. Thus it appears that aureomycin will be found to compare favorably with chloramphenicol in the treatment of rickettsial diseases.

The optimum dose of aureomycin in the treatment of typhus fever is not known. In scrub typhus a dramatic response was achieved with a single oral dose of 3.5 gm.[103] However, until further experience is forthcoming it appears advisable to give an initial dose of between 20 to 30 milligrams per kilogram of body weight over a period of 4 to 6 hours and thereafter a maintenance dose of 0.5 gm. (500 milligrams) every 6 hours until the temperature has been normal for 48 hours. Occasionally one may encounter relapses. In such instances a further single dose of from 1 to 3 grams should be sufficient to overcome the relapse. Epigastric symptoms are encountered rarely if the individual dose does not exceed 1 gm. The administration of 1 fluid dram of aluminum hydroxide shortly after the ingestion of aureomycin has been employed to decrease the incidence of gastrointestinal distress in many patients. However it has been found that aluminum hydroxide definitely decreases the absorption of aureomycin from the gastrointestinal tract. An intravenous preparation of aureomycin hydrochloride is now available. One hundred milligrams of aureomycin hydrochloride and 50 milligrams of sodium glycinate are dissolved in sterile water, normal saline or 5 per cent dextrose solution and given immediately but slowly intravenously. The recommended full dosage is 100 milligrams every 6 hours for an adult. Care should be exercised to prevent extravasation of the solution since it is intensely irritating to tissue. Due to potential venous thrombosis and embolization intravenous administration of aureomycin is not recommended except in moribund patients or others in whom oral administration is impossible. Intramuscular injection should not be used. It is not considered necessary to follow routinely blood levels of these antibiotics during therapy.

There are few toxic complications from the oral administration of

chloramphenicol or aureomycin when given in recommended dosages. Aside from nausea and vomiting already mentioned, patients receiving aureomycin have developed diarrhea or frequent bulky stools. Anal itching is not infrequent.

At the present time the results of the treatment of rickettsial infections of man with chloramphenicol and aureomycin indicate clearly that these two antibiotics are superior to para-aminobenzoic acid. Defervescence occurs much earlier after treatment is begun. Very important is the fact that these antibiotics appear to exert beneficial effect when given late in the clinical course of the disease. The ease of administration in contrast to the arduous regimen imposed by the administration of PABA makes them ideal therapeutic agents for the treatment of typhus fever, particularly under field conditions. Therefore PABA can be recommended currently for use in typhus only when neither chloramphenicol nor aureomycin is available.

Vaccination and Its Effect on the Clinical Course of Epidemic Typhus.—For a number of years killed suspensions of rickettsias have been used for the production of vaccines in various parts of the world. Weigl prepared a vaccine of rickettsias obtained from louse intestines. Although Weigl vaccine has been used extensively with apparent good effect, the laborious method of its preparation has prevented mass immunization. Vaccines have been made from suspensions of rickettsias obtained from mouse lung,[6,77] rabbit lung[8] and dog lung.[9] The preparation of such vaccines made from the lungs of laboratory animals involves considerable risk to the laboratory worker, and numerous laboratory infections with typhus have been recorded.[80,81]

Excluding American, British and Canadian Forces, it is believed that Weigl vaccine and lung vaccine were used probably on a considerable scale for the immunization of medical and sanitary personnel during World War II. The difficulties of extensive production of Weigl vaccine have prevented mass immunization of Armed Forces or civilian populations with this vaccine. To date circumstances have not permitted a comparative study of the preventive efficacy of various types of vaccine except in one instance.[9]

The production of a killed rickettsial vaccine on a large scale was made possible by the cultivation of rickettsias on the yolk sac membrane of developing chick embryos.[82,83] This vaccine, known as Cox type vaccine, improved by the ether extraction method of Craigie,[84] contains the killed rickettsias of the Breinl strain of European typhus. It was produced in steadily increasing amounts throughout World War II.

and was used for the mass immunization of the U S Armed Forces To date one field trial has been reported on the comparison of a Cox type vaccine with Weigl vaccine and vaccines made from dog and rabbit lung This field trial was unsatisfactory in one respect at least, the Cox type vaccine used was made in Germany and unquestionably was much less potent than the American made vaccine A careful appraisal of this experiment leaves little doubt that the protective powers of Weigl Cox type dog and rabbit lung vaccines were demonstrated under rigorous circumstances There was no reduction in the morbidity of the disease but no deaths occurred among the vaccinated group of patients except in a group given diluted yolk sac vaccine whereas the mortality among two control groups was 20 per cent and 33 per cent Among the vaccinated the disease was mild the fever lower and of shorter duration and complications were few

Experience with louse borne typhus among U S Armed Forces during World War II and among laboratory workers in the United States and elsewhere are in agreement with the results of this crucial experiment insofar as the use of a potent Cox type vaccine is concerned There is now no doubt that typhus in persons fully immunized with Cox type vaccine is a greatly modified disease There have been no recorded deaths from typhus among U S Army personnel who have been immunized[c] The fact that a very small number of U S Army personnel considerably fewer than 100 contracted typhus leads one to suspect that vaccination with Cox type vaccine may actually reduce the morbidity of the disease under field conditions Were it not for the extensive use of the louse powder DDT by the U S Armed Forces one would conclude that this were true In this regard the recovery of rickettsias from the blood of vaccinated typhus patients has been difficult and often impossible either by the direct inoculation of blood from patients into animals or by the feeding of lice on patients It is conceivable therefore that the effect of typhus vaccination may play a dual role not only modifying the clinical disease but interfering directly in the dissemination of typhus by interruption of the man louse man cycle

A recent study[88] of louse borne typhus in persons immunized with American made Cox type vaccine has shown that symptoms are milder than in non immunized patients As in non-vaccinated patients chilly sensations may usher in the disease Headache is present almost invariably during the disease but its severity is much reduced Disorientation tinnitus and deafness are seen rarely The fever may be remittent with normal morning temperatures It may never rise above 101° F and its

duration may be less than a week The rash may be absent but usually is seen Most often however it is fleeting in character and may be missed unless searched for at frequent intervals Signs of pulmonary involvement may be absent but when present are minimal and of short duration A palpable spleen usually is present Except in moderately ill patients a decline in blood pressure seldom is encountered Azotemia urinary incontinence and broncho pneumonia are observed rarely

Cases may be seen in which the diagnosis of typhus fever is not even suspected It is therefore necessary to exclude this diagnosis in every mild febrile illness of vaccinated persons living in typhus areas It must be remembered by physicians in this country that air travel makes it possible for a person to leave a louse borne typhus area thousands of miles from the borders of the United States and arrive in this country during the incubation period of the disease In such cases the development of an obsure febrile disease no matter how mild which occurs within 12 to 14 days or possibly longer from the time of leaving a typhus zone may be modified louse borne typhus fever A history of contact with typhus or lice in such instances is important if obtainable The necessity for use of the Weil Felix and complement fixation tests described earlier in this chapter in excluding the diagnosis of typhus also is obvious

The Prevention and Control of Louse Borne Typhus Fever

Factors Contributing to the Spread of Typhus

Epidemics of louse borne typhus are associated with lousiness crowded unhygienic living conditions starvation and the mass movement of populations They reach their peak during the winter and early spring months when cold weather contributes to infrequent bathing and to the massing together of persons for warmth It is clear why great epidemics of typhus have occurred during or following great wars when vast numbers of persons are driven from their homes and are forced to exist under conditions of inadequate food and shelter Such conditions prevailed in many parts of the European continent during and following World War II Aerial bombing forced thousands of civilians to live underground for months at a time Huge air raid shelters housed innumerable persons jammed together in indescribable misery In many instances control of the civilian population by public health

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attendants in a clean hospital ward except from one important viewpoint It must be recalled that the blood of a typhus patient is potentially infectious during the acute febrile period Hospital laboratory workers should be warned of this fact When performing venipunctures on patients reasonable precaution should be taken to avoid contact with typhus blood When the hands of doctors or nurses unavoidably come in contact with such blood the immediate rinsing of the hands in 70 per cent alcohol is advisable Alcohol is a potent rickettsiacidal chemical I do not consider it necessary to wear a mask or gown in caring for hospitalized typhus cases There is good evidence to show that the secretions from the respiratory tract of typhus patients are not infectious so long as they do not contain gross blood I am unaware of any evidence to prove that the urine and feces of louse borne typhus patients require special precautions in handling or disposal As pointed out later the powdering of one s clothes with DDT is recommended when working in hospitals or other places where lice may be present but from my personal experience in the nursing care of typhus patients who have been washed before admission to a louse free ward one need assume no special precautions against infection except contact with typhus blood

The Prevention and Control of Epidemics

The use of a lousicidal agent dichlordiphenyltrichlormethylmethane known as DDT has revolutionized methods of mass delousing for the prevention or control of epidemics of louse borne typhus According to Mooser[4] this compound was synthesized first by Baeyer in Strasburg in 187 but its effectiveness as an insecticide was not appreciated until many years later when Swiss workers used DDT in the control of plant pests and other insects under the trade name neocid It was found then that DDT was a potent lousicidal substance[5] and acted by contact as well as ingestion

In typhus control DDT is used as a powder in 10 per cent concentration In a solvent or emulsified in water it is used for the impregnation of clothes Lice which come in contact with the compound quickly exhibit signs of paralysis which prevents them from biting and death occurs usually in from 6 to 24 hours DDT has no effect on nits There is now evidence that it has no effect on rickettsias in louse feces Powdered DDT retains its lousicidal properties for weeks when applied

authorities disintegrated There was no isolation of the sick, no burial of the dead no delousing and no control over the movements of infected persons When typhus flared up, it spread rapidly to epidemic heights Air raid shelters became a new and potent factor in the epidemiological history of louse borne typhus In a similar manner German concentration camps were a source of epidemics The mass delousing measures employed by the U S Army and Allied Forces prevented great epidemics from beginning and quickly stamped out existing epidemics in territory previously occupied by the enemy

Individual Precautions

Certain individual precautions should be observed when dealing with cases of typhus fever In the first place all personnel, who are liable to contact with cases of typhus or with infected lice should have completed their initial immunization not less than two weeks before possible exposure For immunization the present recommended dose of Cox type vaccine is 2 subcutaneous injections of 1 c c given 10 to 14 days apart This initial vaccination should be followed by a stimulating or booster dose of 1 c c in November and again in February of each year so long as the individual remains in areas where exposure is a possibility

With regard to contact with patients it is important to recall that lice rapidly leave the garments of persons dead from typhus to seek new hosts It is also important to remember that the clothes of typhus patients particularly the underclothes are extremely infectious due either to the presence of lice or to the deposition of infected louse feces While DDT kills lice it has no effect on rickettsias in the excreta of these lice Therefore every measure should be taken to prevent the dissemination of infected louse feces or lice from the clothes or bedding of a typhus patient before they are sterilized Sterilization may be effected by the use of dry heat at 60° C for the period of 1 hour or by soaking garments in a 2 per cent lysol solution for 1 hour The use of steam heat at 100° C for from 1 to 3 hours is effective particularly when dealing with large bundles of clothes bedding or mattresses

Before admission to the hospital every typhus case or suspect case should receive a soap and water bath At this time the hair of the head and body should be shaved These measures remove the danger of lice or louse feces remaining on the skin of the patient A deloused thoroughly washed typhus patient is no longer a source of danger to

3 Individual prophylaxis through use of an insecticide applied at appropriate intervals to clothing as dust or by impregnation
4 Improvement of living conditions with provision for frequent bathing and washing of clothing

B The infected individual contacts and environment

5 Quarantine Exposed lousy susceptibles should be quarantined for 15 days but may be released after application of insecticide with residual effect

C. Epidemic measures

1 Delousing The most important measure for the rapid control of typhus where the reporting has been good and the number of cases small is the application of insecticides with residual effect to all contacts Where the infection is known to be widespread the systematic application of residual insecticide to all persons in the community is indicated
2 Vaccination Of persons in contact with cases
3 *Travellers* Permitted to travel without restraint after thorough application of insecticide with residual effect

Brill s Disease

In 1910 Brill[15] described a group of cases seen in New York City which clinically resembled European louse borne typhus fever At that time he hesitated to term these cases typhus but described their illness as an acute infectious disease of unknown origin In 1911 this investigator believed that the disease was a form of modified European typhus fever[16] In 191 Anderson and Goldberger[1] reported the transfer of virus from patients with Brill s disease to rhesus monkeys and observed that monkeys recovering from an attack of the disease were immune from further infection by the same virus and showed cross immunity to Mexican typhus Since Brill s first description of the disease many cases have been seen in New York Boston and other cities in Eastern United States and Canada Zinsser and Castaneda[18] were able to obtain three strains of rickettsias from patients with Brill s disease which resembled the European louse borne virus Zinsser[13] on the basis of epidemiological and immunological data postulated that Brill s disease is a recrudescence of European typhus Almost all cases occur in Jews

to clothes provided they are not washed. Clothing impregnated with DDT may be washed at least once and still demonstrate noninfestability. Since body lice remain largely in the clothing and only attach themselves to the body while feeding, it is important to apply DDT to the inner layer of the clothing of persons being deloused. However, it is not necessary that they disrobe.

Various types of compressed air, hand or power dusters are used for the application of DDT during the delousing process. These dusters are fitted with nozzles which facilitate the forceful blowing of DDT into the garments of fully clothed persons where lice and nits are found most frequently, i.e. on the skin side of the innermost clothing around the neck, in the axillae, and around the waist and the crotch. Powder is to be applied between layers of garments if more than one layer is worn. Likewise, the hair of the head and head gear are to be dusted. When properly performed this method of dusting covers the entire surface of the inner garments with powder as well as the skin of the chest, back, armpits, thighs and pubic and perianal regions. One and one half to two ounces of powder usually are required for the dusting of one adult.

When dusting is performed in homes, all extra clothing, as well as bedding and mattresses are to be dusted thoroughly. DDT is not toxic when applied to the skin in powder form. For persons engaged in continued dusting indoors a gauze mask is helpful in preventing irritation to the nose and throat.

Present methods for the prevention and control of typhus epidemics are based on (1) the prevention or eradication of lousiness, (2) quarantine and (3) immunization. These three measures were used with dramatic effect in the prevention and control of typhus epidemics during World Ward II, notably in Italy in the winter of 1943-1944 and in Germany and liberated countries in the winter of 1944 and spring of 1945[9].

The experience gained in the prevention and control of typhus epidemics in World War II has been incorporated in the official recommendations of the American Public Health Association[10]. Important aspects of control methods are quoted:

A. Preventive measures

1. Routine application of an insecticide with residual effect at appropriate intervals to populations living under conditions favoring the development of lousiness.
2. Vaccination of exposed populations.

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of European origin who have come from endemic centers of louse borne typhus. The disease is not associated with lousiness.

Zinsser's hypothesis regarding the etiological agent of Brill's disease has been strengthened recently by Murray, Snyder and collaborators[101] In 14 patients with clinical Brill's disease, supported by serological studies these investigators were able to isolate rickettsias in 7 of them which were biologically indistinguishable from known strains of *Rickettsia prowazeki*. Two of the 14 patients died. Other important facts brought out by these studies are that the Weil-Felix test frequently may be negative in patients with Brill's disease and that the laboratory confirmation of the clinical diagnosis should be made by the complement fixation test or the rickettsial agglutination test. Moreover, although lousiness appears not to be an epidemiologic factor in the contraction of Brill's disease these patients can infect human body lice with typhus rickettsia. The implications of this fact regarding possible foci of typhus outbreaks are obvious. Although the mortality rate is low in this disease it should be remembered that patients have died, and therefore prompt treatment with a suitable antibiotic is advisable[103a]

From the clinical viewpoint the disease is indistinguishable from classical louse-borne typhus. Murray and his associates emphasize the fact that when one encounters a foreign-born patient with a fever of unknown origin, who has lived at some time in an area where typhus occurs in epidemic form who suffers from intense, persistent headache and who develops a macular or maculopapular rash on the fourth to the sixth day of illness the diagnosis of Brill's disease can be made correctly in a very high percentage of cases

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March 1 1951

CHAPTER XVI A

RICKETTSIALPOX

By SIDNEY COHEN

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Synonym — Kew Gardens spotted fever

Definition — A specific infectious disease produced by *Rickettsia akari* The typical case is characterized by the successive development of a primary cutaneous lesion fever and a generalized cutaneous eruption

Historical

Rickettsialpox was recognized first in 1946 during an epidemic outbreak of the disease in the Kew Gardens section of the borough of Queens New York City[1 2 3] Subsequently many cases were recognized in other sections of the city where the disease has remained endemic with

a rate of 100 to 150 cases per annum The etiology, epidemiology and specific serological diagnosis were elucidated promptly by a study of the original outbreak The development of rickettsiostatic antibiotics aureomycin chloramphenicol and terramycin, has furnished specific therapeutic agents

Rickettsialpox appeared to be restricted to New York City until the recent observation of the naturally acquired infection in Boston Massachusetts[4]

Etiology

Rickettsia akari is the etiological agent of rickettsialpox Like all the pathogenic rickettsiae it is a minute pleomorphic coccoid or coccobacillary organism which fails to grow on lifeless media but grows readily in the yolk sac of the embryonated hen s egg and in the tissues of susceptible animals notably mice and guinea pigs where it is found both intra and extra cellularly predominantly in the cytoplasm and to a lesser degree in the nucleus

The etiological relationship of *Rickettsia akari* to rickettsialpox was demonstrated by the isolation of this organism from the blood of patients in the acute stages of this disease and by the appearance of antibodies to *R akari* in the serum of patients convalescent from rickettsialpox[6] Additional indirect evidence was furnished by the occurrence of cases of rickettsialpox as the result of laboratory infections in personnel working with *R akari*

Epidemiology

As is the case with most rickettsial diseases rickettsialpox is primarily an infection of animals which is transmitted to man by an arthropod vector The animal reservoir is the common house mouse *(Mus musculus)*

Direct evidence to this effect was supplied as with the human disease by the recovery of *R akari* from house mice and by the demonstration of specific complement fixing antibody in serum from mice trapped in the environment of patients[8] One strain of *R akari* was isolated from pooled livers and spleens of house mice in the Kew Gardens outbreak while two successful isolations were reported from mice in

Boston. Serum from 4 of a total of 7 mice taken in New York gave positive complement fixation tests, while 3 out of 11 mice trapped in Boston possessed such antibodies. On the other hand, mice trapped in Virginia, where human rickettsialpox has not been seen, had uniformly negative complement fixation tests.

The vector of rickettsialpox from the mouse to man is in all probability the blood sucking mite *Allodermanyssus sanguineus*.[10] This mite in the unengorged state is so small as to be barely visible to the naked eye. Apparently it is primarily parasitic upon house mice. *A. sanguineus* evidently is very widely distributed, for it has been detected, usually in houses or apartments, in many widely scattered urban areas in the United States, including Tucson, Arizona, the District of Columbia, New York, Philadelphia, Indianapolis and Boston. In the original Kew Gardens epidemic it was found in large numbers on the basement walls and attached to trapped mice. Two lots of mites taken from such buildings were found to harbor *R. akari*. Investigation of subsequent cases of the disease in other buildings both in New York and in Boston[9] also disclosed many specimens of *A. sanguineus* in close relation to mouse harborages. *A. sanguineus* has been shown experimentally to be capable of transmitting rickettsialpox to laboratory mice.[10] It is a reasonable presumption, therefore, that the mites acquire the infection from mice and transfer the organisms to man in the course of biting. Evidently the bite is relatively painless, for patients give no history of previous insect bite.

The biology of the infection in *A. sanguineus* has not been worked out as yet. Analogies which may be drawn from other tick- or mite-transmitted rickettsial diseases suggest that *A. sanguineus* will be found to suffer no harm from parasitization with *R. akari*. Ticks and mites often are able to transmit rickettsiae from one generation to another via the ovum. Such transovarial passage is of obvious practical importance in maintaining an infectious reservoir. Transovarial passage of *R. akari* has not yet been reported in *A. sanguineus*. However, it has been shown to take place under experimental conditions in *Liponyssus bacoti*, the tropical rat mite.[11]

The possibility of alternative vectors appears to have been explored only in the case of *L. bacoti*. This mite virtually is ubiquitous in both temperate and tropical regions and parasitizes both mice and rats. However, although under experimental conditions it may transmit rickettsialpox in mice, it does not appear to be a very efficient vector.[11]

Epidemiological investigation by Greenberg Pellitteri and Jellison[1] of the original New York epidemic supported the relation between mice and rickettsialpox They found that cases were restricted to dwellers in a large housing development in the borough of Queens Persons living nearby in small houses apparently were free of the disease The individual apartments in the housing development were clean and sanitary However large numbers of mice had been noted by many tenants in basements yards and in some of the living quarters Investigation confirmed the presence of extensive mouse infestation particularly in the basements where multiplication of the mice was favored by an ample food supply in the form of unconsumed refuse in and about inadequately fired incinerators

Following the initial report of the disease scattered cases and groups of cases have been reported from the greater part of the city with the exception of Staten Island The disease now occurs either in single isolated cases or in small epidemics usually restricted to a single apartment house[21]

Rickettsialpox has not shown any consistent seasonal variation Persons of all ages and of either sex appear to be equally susceptible Occupational exposure does not appear to be an important factor Rose[13] noted an unduly high proportion of negroes among his patients a fact which he ascribed to their poor economic status and greater liability to contact with mice

PATHOLOGY

The general pathology of rickettsialpox in man is not well known since fatalities have not been reported The histology of primary and secondary cutaneous lesions have however, been studied in specimens obtained at biopsy[14]

The primary lesion shows a superficial ulcer the base of which rests on a zone of fibrinous exudate and coagulative necrosis in the outermost layers of the dermis Slightly deeper in the dermis there is an inflammatory reaction due to collections of lymphocytes and mononuclear cells The cellular reaction is particularly intense about the sweat glands hair follicles and blood vessels The capillaries in many instances showed thromboses necroses of their walls and hemorrhages The secondary lesion shows some edema of the deeper third of the epithelium and a

cellular reaction in the dermis not dissimilar to that seen in the primary lesion Rickettsiae were not identified in any of these lesions

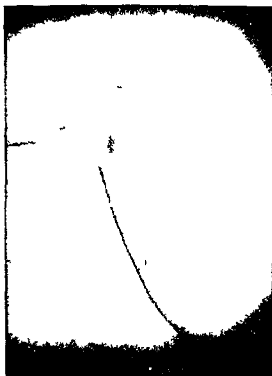


Fig 1 Primary lesion of rickettsialpox on the breast of a 58 year old woman

Symptomatology

The first manifestation of rickettsialpox is a primary cutaneous lesion[1,2,3,13,15,16,17] (Figs 1 and 2) This lesion to be found in 90 per cent or more of patients may be situated on the skin of almost any part of the body with no tendency toward a site of election It has been observed on the face neck abdomen chest (Fig 1) back genitalia and extremities (Fig 2) Occasional patients may exhibit double primary lesions either closely grouped or at widely separated sites such as one on the forehead and another on the abdomen[17]



Fig I rimary lesion of rickettsialpox on the leg of a 7 year old man

The lesion (Figs 1 and) begins as a small firm erythematous papule As this papule increases in size a deeply situated vesicle containing either clear or somewhat cloudy fluid is formed in its central portion

Within a few days the vesicle either ruptures or becomes desiccated and is replaced by a brown or black firmly adherent crust The lesion is neither painful tender nor pruritic and therefore often goes unnoticed by the patient About the end of the first week when the patient usually first seeks medical attention the lesion appears as a shallow round or oval ulcer 0 5 to 5 centimeters in diameter covered by a dark dry adherent eschar The regional lymph nodes are moderately enlarged and slightly tender but lymphangitis does not occur The primary lesion persists with little change through the febrile stage of the disease and heals about one week later leaving a small flat scar Its total duration is about three weeks

Systemic illness usually begins about 7 days after the inception of the primary lesion The incubation period from the time of exposure to the beginning of systemic illness has been 9 to 10 days in a few patients with appropriately limited periods of exposure [1] The onset of symptoms often is abrupt but the disease as a whole is a mild one The marked prostration delirium and vascular collapse typical of more serious rickettsial infections do not occur in rickettsialpox In some cases the patient may not be appreciably disabled and may be ambulatory throughout the illness

Fever is present in all patients (Fig 3) It usually is remittent attaining levels of 10 to 104 F in the afternoons although extreme variations of 100 to 105 6 F are reported The morning temperature often is normal at which time the patient may feel perfectly well only to have symptoms reappear as the temperature rises again in the afternoon The duration of fever in most patients is about 7 days with a range of to 10 days The temperature falls by lysis

Shaking chills often multiple occur in about 50 to 70 per cent of the patients usually during the first two or three days of the illness Chilly sensations and sweats are common

Moderately severe headache is a universal complaint While not so severe as that seen in typhus fever it is more marked than usually is the case in common febrile illnesses The headache usually is frontal or retro orbital rarely occipital or generalized

Malaise muscular pains backache lassitude and drowsiness are com

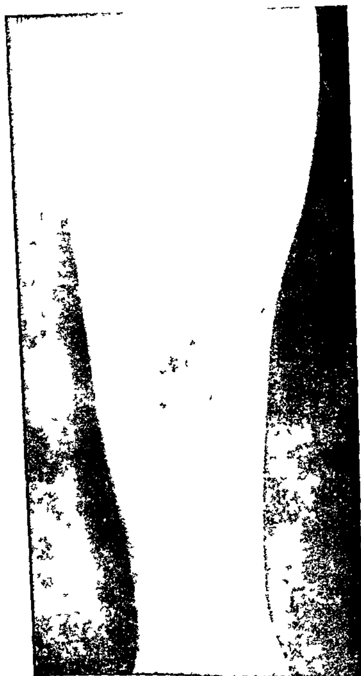


Fig Primary lesion of rickettsialpox on the leg of a 72 year old man

by an erythematous ring (Fig. 5). The enanthem may be of shorter duration than the generalized eruption and may be readily overlooked.

The individual lesion is a bright red maculopapule which, within a day or two, attains a diameter of to 10 millimeters. Most of the papules are rounded, but a few are acuminate. Within or 3 days vesicles may be noted in some of the lesions. These vesicles, which contain cloudy fluid, usually appear as deeply situated, firm, greyish, minute spots in the apices of the papules. In some instances the vesicle may increase in size so as to occupy most of the papule, leaving only a thin circle of erythema at its base. During the later stages of the eruption, some of the vesicles rupture or become desiccated and give way to small crusts.

The fully developed eruption in the individual patient will therefore comprise a mixture of papules, papules containing a tiny vesicle and relatively large vesicles suggestive of chickenpox. The resulting polymorphous appearance is a characteristic feature of rickettsialpox. The total duration of the eruption usually is 4 to 7 days, the lesions involuting shortly after the subsidence of fever. Temporarily pigmented areas may be left behind, but scarring does not occur.

Physical signs other than the rash are meager. The tip of the spleen may become palpable in a few instances. The conjunctivae may be slightly injected.

The blood leukocyte count in 75 per cent or more of patients is depressed, with values between 500 and 5 000 per cubic millimeter. Most of the other patients have normal leukocyte counts, while a rare patient may have a slight leukocytosis. When leukopenia is present there usually is a relative lymphocytosis. Abnormal mononuclear cells resembling those seen in infectious mononucleosis may be found for periods of a day or two in the blood of a few patients.[13] The urine may contain small amounts of albumin during the febrile period. The sedimentation rate of the red blood cells is normal or only slightly elevated. The spinal fluid in the few reported examinations has been normal.

DIAGNOSIS

The specific laboratory diagnosis is made most conveniently through the complement fixation test using antigen prepared from *R. akari*[9, 12, 13] (Table I). This test almost always becomes positive in untreated rickettsialpox. At least two specimens of serum should be tested, one taken as early as possible in the illness, the other in the convalescent period, 2 to 3 weeks after the onset of the illness.

mon complaints during the febrile period Occasional patients suffer pain or stiffness in the neck, photophobia nausea and vomiting

A generalized cutaneous eruption is a feature of all reported cases of rickettsialpox In a few instances however, the eruption may be very faint and its detection may require careful search The eruption usually

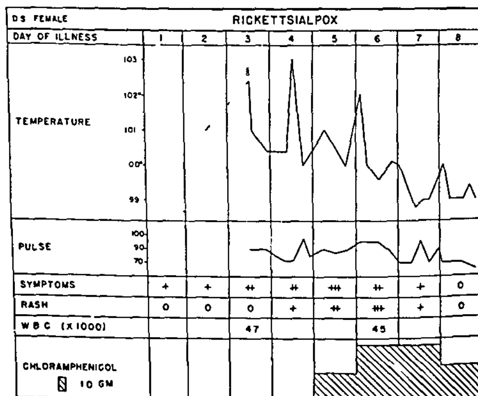


Fig 3 Clinical chart of a case of rickettsialpox due to laboratory infection

becomes apparent during the second third or fourth day of fever but occasionally it may be delayed until the fifth to the ninth day

The eruption may vary from very sparse to profuse but in most instances comprises between 0 and 200 papules The distribution is universal involving the face trunk and extremities without any characteristic order of appearance (Fig 4) Lesions of the palms and soles have been reported but are rare An enanthem may be found in as many as 5 per cent of the patients[17] The lesions appear on the buccal mucosa palate or tongue consisting of a few small vesicles surrounded



Fig 5 Vesicular secondary rickettsialpox on the tongue and the upper lip (From Greenberg M Pellitteri O Klein I F and Huebner R D[8])



Fig 4 Macular and maculopapular secondary lesions of rickettsialpox on body (From Barker L.P[18])

TABLE I

COMPLEMENT FIXATION TESTS IN FOUR CASES OF RICKETTSIALPOX

Patient	Day of Disease	Epidemic typhus antigen	Murine typhus antigen	Q fever antigen	Rocky Mountain spotted fever antigen	Rickettsialpox antigen
E K	8	0	0	0	80	40
	9	0	0	0	160	3 0
	13	0	0	0	560	560
D L S	2	40	0	0	0	0
	7	—	—	—	10	0
	17	160	40	0	80	80
E T	1	0	—	0	—	0
	6	0	—	0	—	40
	10	0	—	0	—	80
	14	0	—	0	—	80
I S	7	0	—	0	—	0
	1[illegible]	0	—	0	—	0
	4	0	—	0	—	40

Figures are the reciprocals of serum dilutions giving 3+ complement fixation The tests were performed by the Department of Microbiology Harvard University School of Public Health Ether-extracted yolk sac antigens were furnished through the courtesy of the Lederle Laboratories

This patient had received epidemic typhus immunization one to two months prior to this illness

Sera collected early in the course of the illness especially during the first 4 days of fever usually will give a negative complement fixation test During the last few days of fever some positive tests appear Two to 3 weeks after the onset of illness virtually all patients give positive tests the usual serum titers ranging between 1 16 and 1 312 Three patients tested 9 to 15 months after their illness still had moderately elevated titers of antibody[13] Such persistence of antibody may be useful in making retrospective diagnoses of rickettsialpox Also it should make one cautious of assigning the diagnosis of rickettsialpox to a recent illness on the basis of a single positive test The demonstration of a distinct rise *in titer of antibody in two successive specimens of serum is,* however good evidence of rickettsialpox

Serological tests to this date do not indicate any significant antigenic variation among different strains of *R akari* One may therefore use only a single strain as antigen for complement fixation tests The interpretation of the complement fixation test may be complicated by antibiotic treatment Rose Kneeland and Gibson have shown that patients treated effectively with aureomycin relatively early in the course of rickettsialpox may fail to develop complement-fixing antibodies In *such patients the only satisfactory laboratory confirmation of the diag*nosis is the isolation of the rickettsia itself

The specificity of the complement fixation test in rickettsialpox is limited by one important cross reaction Sera from over 80 per cent of patients with this disease give positive tests with antigen prepared from *R rickettsii*, the agent of Rocky Mountain spotted fever[8, 13] Usually the titer of the reaction with spotted fever antigen is the same as or somewhat lower than that with the rickettsialpox antigen but occasionally it even may be higher Conversely the sera of patients convalescent from Rocky Mountain spotted fever *also fix complement* with *R akari* but usually with some diminution in titer Minor cross reactions with rickettsialpox serum and typhus fever antigen occur[11] but are too slight to be of clinical importance Cross reactions do not occur with antigens of Q fever or tsutsugamushi fever

Serological differentiation between Rocky Mountain spotted fever and rickettsialpox usually may be made by means of the Weil-Felix test This test measures the agglutinative titer of the patient s serum against certain strains of *B proteus* which have been denominated OX 19 OX-2 and OX K Rocky Mountain spotted fever like most rickettsial diseases induces a positive Weil Felix test with either *B proteus* OX-19 or OX-2 Rickettsialpox on the other hand like Q

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	9	0	0	0	160	3[illegible]0
	13	0	0	0	560	560
DLS	2	40	0	0	0	0
	7	—	—	—	10	0
	17	160	40	0	80	80
ET	1	0	—	0	—	0
	6	0	—	0	—	40
	10	0	—	0	—	80
	14	0	—	0	—	80
IS	7	0	—	0	—	0
	1[illegible]	0	—	0	—	0
	4	0	—	0	—	40

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The cutaneous lesions of rickettsialpox have been confused most often with *chickenpox*. Some of the vesicular lesions of rickettsialpox may be sufficiently large and thin walled as to suggest chickenpox. However, many other lesions will be seen to be either free of vesicles or will contain the small relatively deep vesicle typical of rickettsialpox. The primary lesion of rickettsialpox has no counterpart in chickenpox. The recurrent crops of lesions seen in chickenpox do not occur in rickettsialpox. Fever and eruption usually occur simultaneously in chickenpox, whereas in rickettsialpox fever usually precedes the eruption by 1 to 4 days.

Infectious mononucleosis usually produces a generalized lymphadenopathy in contrast with the localized adenopathy regional to the primary lesion of rickettsialpox. Although cells similar to those seen in infectious mononucleosis occur in rickettsialpox, their duration is short. The skin eruptions occasionally seen in infectious mononucleosis are maculopapular in nature and lack the vesicles of rickettsialpox. The heterophile agglutination test with sheep red blood cells is negative in rickettsialpox and positive in the majority of patients with infectious mononucleosis.

Meningococcemia also produces fever and a skin eruption. The lesions usually resemble those of erythema multiforme or may be petechial, while the vesicles of rickettsialpox are not seen. The leukocyte count in meningococcemia usually is elevated in contrast with the leukopenia almost always present in rickettsialpox.

Rickettsial diseases other than rickettsialpox usually may be excluded on clinical grounds alone. Primary lesions do not occur in *typhus fever* and very rarely in *Rocky Mountain spotted fever*. The cutaneous lesions of these diseases are never vesicular, usually they are smaller than those of rickettsialpox and often become petechial. Patients with typhus and spotted fever usually are much sicker than are patients with rickettsialpox. In the urban environments in which rickettsialpox thus far has been found, spotted fever does not occur. *Q fever* is not accompanied by a skin eruption.

Fievre boutonneuse and *tsutsugamushi fever* are rickettsial diseases in which a primary skin lesion not unlike that of rickettsialpox is seen. However, these diseases are unknown in the United States. Fievre boutonneuse is a variety of spotted fever indigenous to the Mediterranean littoral, while tsutsugamushi fever is native to eastern Asia and some of the islands of the Pacific. Furthermore, the generalized eruptions of these diseases resemble those of typhus and spotted fever and

fever is not accompanied by a positive Weil Felix test with any of the standard *B proteus* antigens The maximal titers reported in the serum of convalescent rickettsialpox patients are only 1 10 to 1 40, levels which are too low to be of diagnostic significance

Isolation of *R akari* by injection of the blood of the patient into laboratory mice is a useful and practicable diagnostic test in institutions possessing adequate laboratory facilities This test is particularly useful in those early cases in which the development of antibody may be blocked by chemotherapy

The following technique has been used with considerable success[1] A sample of sterile clotted blood is centrifuged and the serum removed The clot may be frozen at −70 C and stored for months at this temperature Later it is thawed ground and injected in 0 5 to 1 0 milliliter amounts into groups of 6 to 10 mice The animals in this first passage may show no sign of illness A few mice are sacrificed about the sixth to eighth day after inoculation Smears of the peritoneum spleen and liver are stained by the Machiavello method for rickettsiae The ground spleen and liver are injected into a second group of mice Usually the second passage animals will sicken and some will die between the fifth and tenth day after inoculation Rickettsiae usually are demonstrable readily in the spleen and liver The agent then may be passed serially in mice or fertilized hen s eggs Details of identification of the organisms as *R akari* may be found in the paper of Fuller Murray Ayres and Snyder[9]

Differential Diagnosis

The important clinical diagnostic features of rickettsialpox are the primary lesion and the papulovesicular eruption These features are so characteristic that the clinical diagnosis may be made readily in 90 per cent or more of patients It is a corollary therefore that a careful inspection of the entire skin of the patient should be made by the physician

The most important contribution of the laboratory toward the diagnosis is the complement fixation test Properly performed with acute and convalescent samples of serum this test should establish the diagnosis except for the cross reaction with Rocky Mountain spotted fever antigen Correct interpretation of such cross reactions may be made through the use of the Weil Felix test

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are not vesicular Fievre boutonneuse is reported to induce a positive Weil Felix test with *B proteus* OX-19 while tsutsugamushi fever induces a positive test with *B proteus* OX K

Course and Treatment

The outcome of rickettsialpox is invariably favorable neither fatality nor serious complication has been reported In view of the benign nature of this infection the physician may elect to use symptomatic therapy and await the spontaneous termination of the illness However specific antibiotic therapy is highly effective and may save the patient several days of fever and discomfort The largest reported clinical experience is with aureomycin[19] which in doses of 0 5 to 1 0 gm orally every 6 hours is regularly followed by defervescence and subsidence of symptoms within 24 hours A total of 3 to 4 days treatment is adequate Chloramphenicol has given similar results in a smaller group of patients[19] Terramycin is a highly effective agent against *R akari* both in experimental studies and also in a few cases of the human infection[21]

Prevention

The restriction of cases of naturally acquired rickettsialpox to New York and Boston does not necessarily delimit the scope of this disease The animal host the house mouse and the acarid vector, *A sanguineus* are distributed very widely One may anticipate that the infectious reservoir in mice if not already widely disseminated may readily become so Further serological surveys of the mouse populations of our cities would be desirable to settle this question Regions in which infected mice parasitized by *A sanguineus* are found may of course become the sites of human disease if local conditions favor the growth of a large mouse population in close contact with humans Preventive efforts may be of value in such areas as well as cities where human rickettsialpox is known to occur

Preventive measures should be directed toward mouse control Greenberg Pellitteri and Jellison[11] emphasized proper firing of incinerators and cleanliness of basement areas to eliminate a source of food for mice The use of miticides for the elimination of the presumptive vector would appear to be a worthwhile step

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CHAPTER XVII

ROCKY MOUNTAIN SPOTTED FEVER

By GEORGE T. HARRELL

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Introduction

Rocky Mountain spotted fever one of the rickettsial diseases is a generalized infection of unusual severity which occurs when a human being is bitten accidently by an infected tick Man is involved only incidentally since the disease is primarily an infection of ticks and secondarily one of small animals In all the rickettsioses the arthropod is little affected by the infestation in Rocky Mountain spotted fever it serves as a reservoir in nature as well as the vector

The tolerance of arthropods for rickettsias suggests a very long standing association which might even be called a symbiosis[1] In epidemic typhus the human body louse serves as the vector to transmit the disease from man to man In endemic typhus the rat flea serves as the vector transmitting the disease from rat to rat and from rat to man In scrub typhus the mite is the vector the wild rat and possibly other wild rodents apparently are the natural reservoirs Q(ueensland) fever is a natural infection of wild animals transmitted in nature by ticks which can also transmit the disease to domestic cattle, it is not known exactly how man is infected from animals Rickettsialpox is transmitted by a rodent mite from house mice to man[2]

Rickettsial diseases of man which are related to spotted fever and transmitted by ticks are of world wide distribution Rocky Mountain spotted fever of North America apparently is identical with the disease in South America where it has been called São Paulo typhus In Med

iterranean countries fievre boutonneuse which also is called Marseille fever and escarro nodulaire differs only in the fact that the primary site of inoculation is evidenced by an ulcer In Africa Kenya fever and South African tick bite fever apparently are related to Rocky Mountain spotted fever In other parts of the world North Queensland India and Russia tick borne rickettsioses are often called tick typhus All of these strains of rickettsias appear to be immunologically related[3]

History

Rocky Mountain spotted fever was recognized first in the valleys of the Northern Mountain states The disease apparently was recorded first in 1896 by Major W W Wood who collected descriptions of cases from 8 Idaho physicians and transmitted his report to the Surgeon General of the U S Army[4] The cases occurred in the neighborhood of Boise and in the Snake River Basin they were mild and the mortality was low Maxey of Idaho in 1899 published the first clinical account and gave a vivid description of the symptoms and signs In 190 McCullough of Montana described the virulent form with high mortality which had been recognized for many years in the Bitter Root Valley Later in the same year Wilson and Chowning reported their investigations of the disease in Montana and suggested that it was transmitted by the bite of the wood tick[3] The proof that the disease was transmitted by ticks was offered in 1906 by Ricketts and independently by King in the following year Ricketts demonstrated the occurrence of naturally infected wood ticks in the Bitter Root Valley[4] Ricketts had shown previously that the disease could be transmitted experimentally to guinea pigs and monkeys by inoculating them with blood from naturally infected human beings[5]

Ricketts and his associates made fundamental contributions to our knowledge of the organism the vector the mode of infection and the immunology of the disease and sketched in broad outline the mode of attack on the problem Wolbach in 1919 published his classic studies on the etiological agent and the pathology of the disease in ticks and human beings[6] His careful and exhaustive microscopic studies demonstrated among other findings the intranuclear multiplication of the rickettsias in tick tissue The understanding of the abnormal physiological changes in man resulting from the infection and the design of a rational approach to therapy are based on Wolbach's research

EPIDEMIOLOGY

Organism

The rickettsia of spotted fever, like all rickettsias, is a tiny microorganism which is found intracellularly but which requires special staining methods for its demonstration. Wolbach named the organism *Dermacentroxenus rickettsi*, and most authors follow this nomenclature. Bengston in Bergey's Manual of Determinative Bacteriology calls it *Rickettsia rickettsii (Wolbach)*.[9] Pinkerton has discussed the classification and the nomenclature of all the rickettsias and summarizes the viewpoints of Philip and others.[10]

In smears of mammalian tissues the organisms are pleomorphic and may appear as minute paired organisms, lanceolate in shape, surrounded by a narrow clear zone or halo and resembling a pair of pneumococci; or they may be seen as slender rod-shaped forms sometimes exhibiting polar granules. The Giemsa, Machiavello and Castaneda stains each bring out different characteristics. Like other rickettsias, the organisms stain poorly by the usual techniques and appear gram negative. The number of rickettsias found within cells is smaller in mammals infected with spotted fever than in those infected with typhus. The organisms are found predominantly within the nuclei of cells, a very unusual location for micro-organisms; they are found also in the cytoplasm in small numbers.[1, 2, 3, 4]

In the tick there are bacillary, curved and club-shaped forms, smaller rods with deeply staining chromatoid granules and more deeply staining lanceolate forms (Figs. 1 and 2). A very minute form may appear in tightly packed masses in the nuclei of certain cells.

The organism will grow and reproduce only in the presence of living cells. In tissue cultures of mammalian cells grown in plasma the optimum temperature for growth is 32° C.; in fertile hens' eggs the optimum temperature for growth is 35° C. The organisms will remain viable for a short time in ordinary bacteriological culture media, in blood or in infected tissue kept at room temperature without special means of preservation. They may be preserved in the frozen state for months. The organisms are inactivated readily by moist heat and are destroyed by a temperature of 50° C. in 10 minutes. A wide variety of chemical disinfectants readily kill the rickettsias. The organisms are susceptible to drying and are destroyed by desiccation in 10 hours. The spotted fever

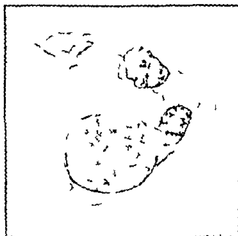


Fig 1 Drawings showing intranuclear growth of *Dermacentroxenus rickettsi* in a cell from the rectal sac of an infected tick (Courtesy of Dr S B Wolbach)



Fig 2 Drawing of a smear preparation of *Dermacentroxenus rickettsi* from the gut of an infected tick (x 1500) (Courtesy of Dr S B Wolbach)

strain of rickettsias does not pass the usual Berkefeld filter candles or Seitz filter pads

Vector

This rickettsial disease is primarily an infestation of ticks. The organism induces no cellular reaction in the tick and apparently does it no harm. The rickettsias are passed to the eggs of the adult female by copulation with an infected male or by infection from the maternal generative organs during cell division and formation of the egg. Thus the vector may be infected at all stages, a distinctive feature of the spotted fever strain of rickettsias. The life cycle of the tick is very complicated and the rickettsias show a cyclic morphology in the various stages; the nuclei of cells of almost all tissues are invaded in all stages of the life cycle. While a large variety of ticks are experimentally capable of transmitting the disease in the laboratory, only ticks found infected in nature are epidemiologically important. The wide geographic dispersal of the proved and potential vectors is discussed by Cox[3].

The association of the wood tick, *Dermacentor andersoni*, with the transmission of the disease was recognized in 1902 by Wilson and Chowning. This tick is found throughout the Rocky Mountain region and adjacent areas. *Dermacentor variabilis*, the American dog tick, is found in the Great Plains region and eastward to the Atlantic coast; to the south it reaches into Mexico; in Canada it occurs eastward from southern Manitoba to Labrador[11]. These two species of ticks are the chief vectors for transmission of the disease to man; their life cycles may cover years.

The larval form may be infected congenitally by transovarian transmission. Since it feeds on a great variety of rodents and certain small carnivors, some of which are susceptible to spotted fever, it may also acquire the infection in this manner. Few larvae survive the complicated life cycle, however. The nymphal form hibernates through the winter. It feeds on many varieties of rodents including rabbits. Nymphs occasionally have been found attached to children. The adult tick bites man readily, although it mainly infests large wild and domestic animals; *D. variabilis* occurs in abundance on dogs, for instance. The adult ticks hibernate through the winter.

The percentage of infected ticks in an endemic area is not great; it varies from year to year in each area but usually is in the range of 3 per cent[7]. The wood tick becomes active during the spring and early summer as the snows melt but may retreat to shady areas and become less active in hot midsummer. The dog tick appears in late spring and remains active longer during the summer. In the South occasional ticks have been found active during the winter.

Ticks live on moist ground covered with small bushes and shrubs where numerous small and large mammals serve as hosts and as a source of blood for food. They hang from the lower branches of the vegetation waving their legs and transfer with great rapidity to the hair of passing warm blooded animals. The presence of blood in the intestinal tract of the tick for [illegible] to 8 hours apparently stimulates the virus in some fashion so that its virulence and infectivity are increased. The period of attachment required for activation of the rickettsias is greater in the early spring than in midsummer when the organisms have reached maximum virulence for the season.

The rabbit tick *Haemaphysalis leporis palustris* does not attack man but is important in the epidemiology of the disease because it feeds on rabbits[12]. Rabbits infected by this tick may transmit the rickettsias to the immature forms of *D andersoni* and *D variabilis* which feed simultaneously on the rabbit host. The rabbit tick completes its life cycle in one year and consistently carries an extremely mild strain of spotted fever rickettsias. It is prevalent in the northern United States and is active from early spring to early fall but in the South the period of activity is considerably extended.

Mammalian Reservoir

In spite of the extensive research done on rickettsial spotted fever over many years no naturally infected animal has been found in the United States. Jellison has pointed out the close geographical relationship which exists between cases of spotted fever in human beings and one species of cottontail rabbit *Sylvilagus nuttalli*; this evidence is circumstantial and was accumulated only for 11 states in the northwestern United States[13]. Many mammals can be infected experimentally with spotted fever rickettsias. When the disease is transmitted experimentally to young dogs and certain other mammals the infection may be very mild with no visible diagnostic lesions or distinctive febrile reaction; immunologic tests however will demonstrate the development of a positive Weil Felix reaction or of complement fixing or other antibodies.

In Brazil the opossum rabbit guinea pig and domestic dog have been found naturally infected. In the Mediterranean area the evidence indicates that dogs are probably the chief animal reservoir. Naturally infected dog ticks have been removed from dogs in the houses of patients with Kenya fever[3].

Clinically and pathologically the disease in animals duplicates that in man to a greater degree than any other infectious process, this statement is true irrespective of the manner of infection — tick bite, feeding of infected material or subcutaneous or intraperitoneal inoculation with infected blood The pathological studies in animals indicate that the disease distinctively involves the blood vessels, chiefly of the skin and central nervous system[4]

Distribution of Cases

Rocky Mountain spotted fever occurs in endemic form throughout most of the United States For many years it was regarded chiefly as a disease of the Rocky Mountain and Pacific states although occasional cases were reported in the North Central area The disease was identified in the East in 1931[11] As is often true recognition of the disease has led to more accurate reporting of cases It is not likely that spotted fever has spread recently from the West to the Eastern and Central states probably it has been endemic in these areas for many years The disease has not been reported from Vermont To judge by the number of cases reported during the period from 1939 to 1947 spotted fever must be quite rare in Arizona Florida Maine, Michigan Minnesota Nebraska New Hampshire Rhode Island and Wisconsin Some cases reported from these states are known to have been contracted elsewhere

TABLE I

CASES 1939 1947

		1939	1940	1941	194	1943	1944	1945	1946	1947
West	Wyoming	4	61	8	38	3	30	14	13	9
	Montana	32	3	107	41	[illegible]8	5	2	9	6
	Colorado	16	10	21	16	1	8	13	10	11
East	Virginia	50	46	33	47	56	81	99	9	67
	Maryland	[illegible]	55	45	59	58	64	47	58	66
	North Carolina	41	3	0	35	36	59	57	66	88
United States Total		560	457	51[illegible]	499	4[illegible]7	4[illegible]0	4[illegible]5	589	553

The cases reported annually to the United States Public Health Service from three states in the East and in the West where Rocky Mountain spotted fever is most prevalent are recorded for comparison with the figures from the United States as a whole

The total number of cases reported in the United States as a whole has remained reasonably constant during the period from 1939 to 1947 it averaged around 500 cases yearly (Table I) The two important endemic foci at present are the Rocky Mountain area — Wyoming Montana and Colorado and the South Atlantic states — Virginia Maryland and North Carolina The number of cases reported in the West especially in Montana and Wyoming began to decline around 1944 probably as a result of the application of effective preventive measures the number of deaths has not declined in the same proportion as the number of cases The mortality remains fairly high throughout the United States, averaging 23 per cent in 4 033 cases reported during the period from 1939 to 1946 (Table II)

TABLE II

Mortality 1939 1946

	Cases	Deaths	Mortality Per Cent
Wyoming	317	58	18 3
Montana	260	63	24.2
Colorado	106	26	24 5
West	683	147	21 8
Virginia	504	9	18 2
Maryland	458	86	18 7
North Carolina	346	96	27 7
East	1308	274	20 9
United States Total	4033	9 9	23.0

The United States Public Health Service reports for the three states in the East and in the West where Rocky Mountain spotted fever is most prevalent have been summarized for comparison with the figures for the United States as a whole

The severity of the infection in any given area remains fairly constant even though it may vary widely in adjacent areas of essentially similar geographic characteristics For instance the mortality in unvaccinated adults in the Bitter Root Valley of Montana has been for years more than 80 per cent when the disease was more prevalent in southern Idaho the mortality was less than 5 per cent This variation reflects the inherent difference in the virulence of local strains There are however in any given area fluctuations in the number of cases and in the mortality from year to year These are influenced more by the weather and hence the appearance and activity of ticks than by variations in the organisms

of the possible reservoirs The fluctuations in severity from year to year are illustrated by the figures for North Carolina, where one of the more virulent strains is found Between 1938 and 1947 in roughly comparable numbers of cases the mortality has varied from 19 to 36 per cent The death rate in the areas where the disease is most prevalent in the West and East as compared with the United States as a whole is given in Table II

Throughout the United States more cases occur during the month of July than in any other, cases are fewest from December through February In the West the majority of the cases appear between April and June in the East the disease is most prevalent during July and August with moderate numbers of cases reported in June and September Scattered cases may occur earlier or later, depending upon the severity of the winter and whether the seasons are early or late

The age distribution of the cases in the various areas reflects the occupational activity of the population and the proximity of the vector to human habitations Few cases are contracted in the city In the sage brush and desert regions of the western United States most infections occur in men who work there the year around sheepherders hunters trappers prospectors miners surveyors highway and railroad maintenance workers and forest service personnel Occasional visitors such as fishermen campers tourists and picnickers will sometimes contract the disease

In the East since the vector is the common dog tick which infests household pets the disease is predominantly one of children and is contracted in suburban or rural areas Many cases occur in vacationists or people seeking recreation Of 576 cases reported in North Carolina during the period from 1938 to 1947 215 were in children under 10 years of age, 113 in the 10 to 19 year age group -8 in adults 20 to 29 years old, 59 in the group from 30 to 44 years and 59 in persons over the age of 45 In children the incidence of cases was higher in females in adults the incidence was greater in males Taking all ages into consideration however the cases were distributed rather evenly between the sexes

Pathological Anatomy

Rarely in any disease are the pathological lesions correlated so closely with the clinical picture in the patient during life The gross appearance of the specimens at autopsy often is not impressive Since the disease is

one which diffusely involves the smallest blood vessels the lesions are found in the microscopic preparations A careful study of the patient's clinical record will reveal a very close correlation between the microscopic findings and the physiological disturbances although the latter may be out of all proportion to the visible anatomical lesions

Gross lesions are found predominantly in organs derived embryologically from ectodermal structures[15] The skin in addition to the rash may show areas of necrosis and gangrene resulting from interference with the arterial blood supply or from ischemia caused by pressure over bony prominences The central nervous system grossly may show few lesions in comparison to the clinical neurological disturbances The damage to the brain however is greater in spotted fever than in any other rickettsial disease

Fluid exudates into the serous cavities as well as the edema of subcutaneous and other less firmly organized tissues reflect the physiological disturbance in the circulation In general pulmonary changes are not striking when death occurs within the first 10 days of the disease later congestion and serous exudation are present almost regularly often with areas of consolidation

In about one third of the cases the *liver* shows distinct swelling cloudiness and opacity of the parenchyma The cut surface may have a nutmeg appearance or a yellowish color occasionally with subcapsular streaking but no softening or focal areas of necrosis are noted grossly The spleen regularly is enlarged, the splenic pulp is firm and tends to bulge from the cut surface but in cases of long duration it becomes friable

The *kidneys* usually are normal in size although the parenchyma may be congested and slightly swollen The cortex usually is pale and rather opaque petechial hemorrhages may be noted beneath the capsule but more frequently they are seen in the medulla and pyramids The *heart* generally is of normal size Any dilatation observed usually is confined to the right ventricle or right auricle Petechiae are noted more often under the epicardium than elsewhere Many times the muscle of both ventricles feels flabby In spite of the vascular character of the disease however no areas of thrombosis and necrosis simulating coronary occlusion or myocardial infarction have been described

In about half the cases purpuric foci are seen somewhere in the mucosa of the *gastrointestinal tract* One of the 5 patients on whom autopsy has been performed in the North Carolina Baptist Hospital died from a fatal gastrointestinal hemorrhage which arose to judge by the

character of the blood in the stools, from the lower part of the small intestine or from the right colon, no gross lesion was observed at autopsy, however

Microscopically the skin and subcutaneous tissues are the best locations for study of the lesions in the blood vessels, and rickettsias can be demonstrated there most easily Detailed descriptions of the lesions are given by Wolbach[1] The rickettsias first invade the nuclei of endothelial cells in capillaries, where they multiply in great numbers and destroy the cells From there the lesions extend centripetally along the intima into slightly larger vessels the arterioles, where smooth muscle cells of the media also are invaded and destroyed a distinctive feature of the Rocky Mountain spotted fever strain of rickettsias (Fig 3) Extension into

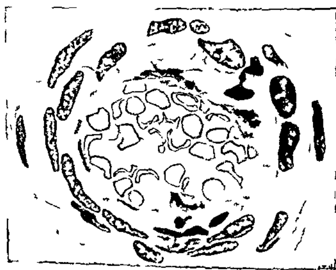


Fig 3 Drawing of a cutaneous artery from a case of Rocky Mountain spotted fever showing rickettsias in the endothelial cells of the intima and smooth muscle cells of the media (courtesy of Dr S B Wolbach)

larger blood vessels arteries occurs to a greater extent in spotted fever than in the other rickettsial diseases in which vessels larger than arterioles are rarely affected The venules are involved to a much smaller extent The lymphatics are not attacked

With the death of cells necrosis occurs in the intima and media of the vessels, resulting in thrombosis and extravasation of blood The thrombi are hyaline and are composed of cellular and nuclear debris rarely of fragmented or intact neutrophils (Fig 4) As a result of the

thrombosis micro infarcts are formed chiefly in the skin subcutaneous tissues and central nervous system The rash in the skin and the petechiae seen in internal organs are the result of extravasation from the necrotizing lesions

The proliferative character of the vascular lesions, as indicated by the presence of numerous mitoses in cells and by perivascular accumulations of mononuclear macrophages has perhaps not been sufficiently stressed (Fig 5) Indeed in one case seen at autopsy in the Baptist

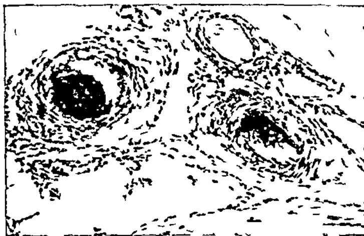


Fig 4 Photomicrograph showing cross sections of cutaneous arteries and veins from a case of Rocky Mountain spotted fever Note the beginning thromboses and early proliferative reaction in the arteries the veins are not affected (courtesy of Dr S B Wolbach)

Hospital series a child of 4 years dying on the eleventh day of rash, the lesions were strikingly similar to those described in periarteritis nodosa While it is true that this particular patient had received therapeutic antiserum and that similar changes have been described in serum sickness lesions of the same general character can be found in cases which have not received specific immune therapy

In specific organs the diffuse character of the microscopic lesions reflects the fact that the most widely distributed blood vessels the capillaries are the site of the first localization of the rickettsias Areas of demyelinization without cellular infiltration or exudation can be found in the central nervous system in association with arterioles or slightly removed from them The focal lesions or nodules in the brain and meninges result from the proliferative reaction

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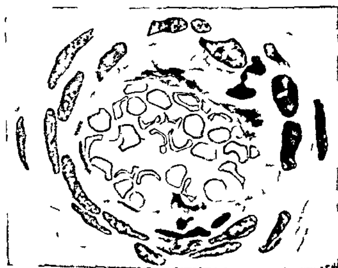


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larger blood vessels arteries occurs to a greater extent in spotted fever than in the other rickettsial diseases in which vessels larger than arterioles are rarely affected The venules are involved to a much smaller extent The lymphatics are not attacked

With the death of cells necrosis occurs in the intima and media of the vessels resulting in thrombosis and extravasation of blood The thrombi are hyaline and are composed of cellular and nuclear debris rarely of fragmented or intact neutrophils (Fig 4) As a result of the

sionally containing fine droplets of fat The location of the lesions in the kidney as well as in other blood vessels suggests that the rickettsias settle out of the circulating blood and parasitize endothelial cells in locations where the blood flow loses speed in the transition from arteries to capillaries Few lesions are found in the adrenals a fact which confirms the impression obtained from physiological studies that the circulatory collapse arises in the peripheral circulation

Pathological Physiology

The physiological disturbances observed in the patient reflect accurately the anatomical damage caused by the rickettsias However the degree of disturbance especially in the circulation may be quite out of proportion to the severity and number of anatomical lesions

In the severe fulminating infections where death occurs in the first few days of the disease the body defenses are overwhelmed by the toxic products of the organisms The clinical picture may be that of peripheral vascular collapse shock apparently resulting from dilatation of the peripheral capillary bed and pooling of blood without alteration in the permeability of capillaries loss of fluid into extravascular spaces or edema Early in the course of less severe infections dehydration and loss of electrolytes from the circulation as measured by blood chlorides are common, the dehydration is accompanied by little change in the plasma volume and extravascular fluid (thiocyanate space) unless crystalloids glucose and saline solutions are administered in large quantities[1, 18]

As the thrombotic and proliferative phase of the lesions develops interference with the flow of arterial blood leads to ischemic necrosis infarction and the resultant secondary effects of anoxia Anoxemic necrosis resulting in decubitus ulcers on the back may be produced by pressure alone without relation to vascular lesions Most areas of necrosis and gangrene in the skin particularly those occurring in the extremities and scrotum result from vascular occlusions

The microinfarcts in the brain disturb the cellular metabolism and produce the clinical picture of encephalitis convulsions tremors loss of memory and alteration of the reflexes The hyperesthesia of the skin and tenderness of the muscles which are quite vascular and show few anatomic lesions may reflect disturbances in the circulation to peripheral nerves the responsible lesion is difficult to demonstrate by anatomical techniques but it is a true peripheral neuritis The sequelae which per-

In the lung the bronchi are often filled with pus and surrounded by pneumonic involvement in which gram positive cocci in fair numbers can be stained Small areas of interstitial infiltration with some inflammatory reaction can be found in the myocardium usually related to the smallest arterioles or capillaries In patients dying in the second week of the disease cellular infiltration is more marked in the epicardium and the adjacent muscle



Fig 5 Photomicrograph showing a tangential section of a cutaneous artery from a case of Rocky Mountain spotted fever Note the thrombosis and necrosis of the artery with the perivascular accumulation of leukocytes and the proliferative reaction (courtesy of Dr S B Wolbach)

In the liver congestion is associated with the accumulation of fine fat droplets in the cells of both the central and the periportal areas Occasionally a few scattered minute focal necroses are seen The involvement of the generative organs frequently noted in Rocky Mountain spotted fever is an unusual feature of rickettsial diseases it occurs to a greater extent in males than in females The reticuloendothelial system shows some degree of hyperplasia the character of which is often altered especially in the spleen by secondary bacterial infection

The involvement of the kidney usually is confined to scattered nephrons the lesions being most marked in the region of the convoluted tubules, interstitial and perivascular infiltration by lymphocytes is found The epithelial cells of the tubules are swollen and finely granular occa

The drop in blood proteins progresses very rapidly The degree of protein destruction can be followed by serial determinations of the amount of nitrogen excreted in the urine[17] In some children the amount destroyed daily has been equivalent to 3 to 6 gm of protein per kilogram of body weight It is not known how much of the protein escapes from the vascular tree into the interstitial spaces through the damaged capillaries In any event the reduction in the circulating serum proteins especially in the albumin fraction lowers the intravascular osmotic pressure and sets the stage for the subsequent development of peripheral circulatory collapse In addition damage to the liver may reduce the synthesis of new protein so that replenishment is decreased and destruction is increased simultaneously Replacement therapy with preformed protein is therefore indicated under certain circumstances

The alteration in capillary permeability is corrected when recovery begins the blood volume is quickly restored to normal within one or two days after the temperature drops and the toxemic symptoms decrease but the loss of edema may take as long as a week and the restoration of circulating blood proteins even longer

When the quantity of fluid confined within blood vessels and found in the extravascular spaces is compared with the changes in weight of the individual a disproportion is found frequently The comparison suggests that the permeability of cells outside the vascular tree may be altered also so that fluid accumulates within body cells as well as in the interstitial spaces[18] This excessive hydration of cells may affect the function of organs in which vascular lesions are not pronounced The observation of stupor tremor and medullary respiratory arrest which is seen occasionally in fatal cases, is clinical evidence that nerve cells are hydrated excessively, the increase in cerebrospinal fluid pressure in such instances usually is less than would be expected if the cerebral edema were entirely interstitial Unfortunately no technique is available at present for the measurement of intracellular fluid Regardless of whether the fluid goes into tissue spaces or into cells the loss from the circulating intravascular fluid lowers the blood volume and precipitates peripheral circulatory collapse

The mechanism responsible for the alteration in permeability of membranes at the peak of the disease is obscure The maximum changes in capillary permeability occur at the time when immunity should be rising rapidly and beginning to attain ascendancy over the infection The alterations usually appear at the end of the second week (the time required for the development of antibodies) and the subsequent clinical

sist such as scars in the skin loss of memory or mental power and permanent neurological changes, mirror the damage in organs which canno regenerate or adequately repair themselves

The myocardial damage can be detected by serial electrocardiograms but is not often sufficient to cause frank congestive failure unless the circulation is overloaded by too enthusiastic fluid replacement therapy[18] The changes in the electrocardiogram which have been observed are similar to those occurring with edema due to beriberi myxedema or anasarca from other causes Pathologically sections of the myocardium in fatal cases usually will show, in addition to interstitial cellular infiltration some edema of the muscle fibers, in other fatal cases lesions resembling periarteritis nodosa have been seen in small blood vessels Two mechanisms may be involved in the myocardial failure, mechanical interference resulting from edema and anoxia resulting from the involvement of arterioles

The scattered character of the renal lesions, involving individual nephrons is reflected in the irregular and slight physiological renal disturbance as measured by the usual function tests The elevation of the blood nonprotein nitrogen early in the course of the disease is due to inadequate glomerular filtration resulting from dehydration, when circulatory collapse is imminent the low blood pressure further reduces glomerular filtration and increases the extent of the prerenal azotemia

The involvement of the individual liver cells is reflected by a reduction in some phases of liver function during the third week of the disease and during early convalescence, the fact that the cells are physiologically damaged and not destroyed is proved by the return of complete function in late convalescence The administration of a high protein diet from the first seems to prevent or greatly reduce the alteration in liver function

A rough general correlation is observed between the petechial character of the rash the clinical severity of the disease and the extent of edema Apparently the permeability of membranes especially those comprising the walls of capillaries is altered progressively as the disease increases in severity, so that water crystalloids proteins and red blood cells are passed The alteration is greatest near the clinical peak of the disease between the tenth and fourteenth days of rash at this time there is a tendency for the plasma volume and serum proteins to drop, the thiocyanate space to rise and clinical edema to develop These alterations can be accelerated by the excessive administration of crystalloids alone



Fig 6 Edema in a 14 year old boy treated with serum and PABA the clinical course is summarized in Fig 11

Top Seventh day of rash Note the marked edema and the hemorrhagic diffuse character of the rash

Bottom Sixteenth day of rash Note the subsidence of the edema producing wrinkling of the great toe and the fading of the rash

The application of these principles to supportive therapy is discussed further in the section on Therapy

improvement would suggest that the immune balance is being tilted The neutralization of antigens by antibodies either circulating or fixed to tissue cells must produce a substance which directly affects membranes It has been known for years that antigen-antibody reactions liberate a histamine like substance That histamine and similar substances alter capillary permeability is readily demonstrated by the production of a wheal when histamine is injected into the skin Our observations suggest that the antigen antibody effect involves the general circulation and alters the permeability of the entire vascular tree

The similarity of some of the microscopic pathological lesions in cases of Rocky Mountain spotted fever to those of experimental serum sickness is intriguing In our experience the patients in whom such lesions are most pronounced have been those who have received hyperimmune antiserum Since immune bodies are found in the globulin fraction of serum the chance presence of immune bodies to rickettsias in blood or plasma might explain the transfusion reactions observed occasionally in patients with rickettsial spotted fever The development of antihistaminic drugs raises interesting therapeutic implications which will be discussed further in a later section

Because rickettsias are located intracellularly, one would expect cellular as well as capillary permeability to be increased It is known that cells participate in the immune process and are affected by allergic or immune manifestations An antigen-antibody reaction occurring within the cell might be expected to liberate a histamine-like substance which would increase the permeability of the cell membrane In patients with spotted fever it is difficult to obtain an adequate quantity of interstitial fluid for chemical examination by the insertion of needles subcutaneously In view of the ease with which fluid can be obtained from patients with congestive failure the suspicion that some of the fluid lost from the circulation may be found within cells as well as between them is strengthened

The alterations in permeability are evidently reparable with the full establishment of immunity this conclusion is based on clinical observation alone however since no quantitative data on the degree of immune response have been obtained experimentally The diuresis which regularly occurs with recovery from infectious diseases including spotted fever has been known to clinicians for years though the mechanism has never been explained The restoration of capillary and cellular integrity would enable interstitial and intracellular fluids to be mobilized and excreted through the kidney (Fig 6)



FIG 6 Edema in a 14 year old boy treated with serum and PABA the clinical course is summarized in Fig 11

Top Seventh day of rash Note the marked edema and the hemorrhagic diffuse character of the rash

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Natural History of the Disease in Human Beings

Exposure

A history of a trip into a known endemic area, of exposure to ticks in the woods, fields and ranges or of exposure in the handling of dogs or sheep may be obtained. It may be important to know how the tick was removed, whether it was crawling or attached and whether it contained blood. Children of course may not notice the tick, or, while they are ill they may not recall having been bitten. The bite is painless, and no local lesion is produced.

Rickettsias may remain alive in fresh or dried tick feces for a matter of hours. It is possible that rickettsias contained in feces deposited by ticks on dogs or sheep may enter the circulation of the human victim through scratches or other minor abrasions. This means of infection may account for the failure to obtain a definite history of an attached tick in a moderately high percentage of cases. Infection in laboratory workers is not rare. However, cross infection from one individual to another through the medium of blood or excreta is practically unknown.

Symptoms

The symptoms to be described are characteristic of the disease as it occurs in unvaccinated patients treated only with supportive therapy. In cases where an attached tick containing blood was found, the incubation period has varied from 2 to 14 days, it tends to be shorter, 5 days or less in the more severe infections and longer in the milder ones. In areas where ticks are prevalent the great number of the insects and the frequency with which they are found on the person make it difficult, if not impossible, to determine the exact time of infection.

The prodromal period may extend over 2 or 3 days and the gradual appearance of symptoms may make it difficult to establish exactly the date of onset. Among the symptoms which may be noted during this period are headache, malaise, loss of appetite, photophobia, chilly sensations, low fever and pain in the muscles and joints. On the other hand the onset may be precipitous, characterized by a distinct shaking chill, severe headache, marked lumbar backache, abdominal pain, vomiting, sweating and even diarrhea. It is usually impossible to make a diagnosis on the basis of symptoms alone.

As the disease progresses mental clouding and generalized tenderness become more pronounced obscuring most other symptoms

Rash

The appearance of the rash is the earliest dependable diagnostic sign It may appear on the day following the onset of symptoms but usually is delayed 3 to 4 days Because the onset of symptoms frequently is indefinite it is more accurate to date the course of the disease from the day the rash appears The rash usually is noted first on the ankles and feet spreading within a matter of hours to the wrists and hands and then gradually toward the trunk and head (Fig 7)

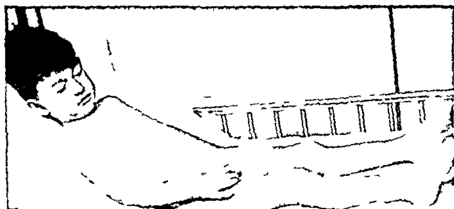


FIG 7 Twelfth day of rash in a severely ill 4 year-old boy who was treated with serum Note the edema and the preponderance of the lesions on the extremities and face

When it first appears the rash is macular red and flat, it blanches with pressure and may resemble measles It is more easily seen when the temperature is elevated Within hours it becomes papular darker red and slightly dusky in hue It becomes fully developed within 2 to 3 days assuming a definitely petechial or purpuric character Fading on pressure no longer occurs The hemorrhagic character of the rash can be accentuated or brought out before it spontaneously appears by applying for 3 to 5 minutes a tourniquet or a blood pressure cuff inflated to a level between the systolic and diastolic pressures (Rumpel Leede phenomenon) (Fig 8)

Other Physical Findings

Once fever has appeared the *tempera ure* rises quickly The height which the temperature attains frequently is not appreciated Of 46 cases treated in the North Carolina Baptist Hospital from 194 to 1947 three fourths had temperature peaks above 104 F (40° C) Almost half had temperatures above 105 and 5 patients had peaks higher than 106° F (41 1 C) Hyperthermia may be a poor prognostic sign though all five of our patients with temperatures of 106 or above survived The character of the temperature curve was high and spiking with irregular morning remissions, often as much as 3 to 5° F in 28 cases, high and sustained in 11 and moderate or low in the remainder In general children tend to run higher temperatures than adults

Usually the maximum temperature will be reached during the second week of the disease anywhere from the seventh to the fourteenth day With recovery the temperature usually falls by lysis after a febrile period varying from 2 to 3 weeks (Fig 9) A secondary rise in temperature after one peak has been attained frequently heralds the development of a complication usually pneumonia

At the onset and early in the course of the disease the *p lse* is full and strong but as the disease progresses it may become weaker or even thready In adults the pulse in general tends to parallel the temperature or run slightly below it, no adults in the Baptist Hospital series had pulse rates above the corresponding temperature The majority of children below the age of 15 had a pulse rate higher than the temperature in only about 15 per cent of the children in the Baptist Hospital was the temperature higher than the pulse A relatively high pulse rate from the onset is often an unfavorable sign A sudden elevation in pulse rate within a 24 hour period usually indicates the appearance of a complication circulatory failure In our series the development of pneumonia did not cause the pulse rate to rise A terminal rise in the pulse rate was observed during the last 1 to 3 days of life in approximately a third of our fatal cases

The *respiratory rate* at first is normal or only slightly increased A slight nonproductive bronchial type of cough is frequent at the onset and probably is caused by organisms settling out in the filter bed of the lungs Rales may develop later in the disease as a result of true rickettsial pneumonia pulmonary interstitial edema or secondary bacterial pneumonia Near the peak of the disease pulmonary congestion may occur as a result of myocardial failure

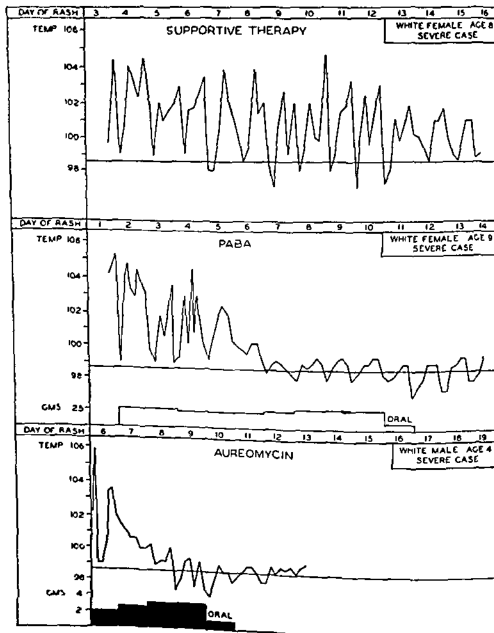


FIG 9 The course of Rocky Mountain spotted fever in children
Top With supportive therapy alone
Middle With PABA and supportive therapy
Bottom With aureomycin and supportive therapy
(This chart was first reproduced in the *Southern Medical Journal* January 1949)



Fig 10 Edema in a 4 year-old girl treated with supportive therapy
Left One month after onset Note the absence of edema
Right Eighth day of rash Note the pronounced edema with closure of the eyes and puffiness of the hands

The *blood pressure* usually is normal at the onset but later becomes variable The pulse pressure frequently tends to decrease with a con comitant drop in both the systolic and diastolic levels as the peak of the disease is reached The blood pressure may drop suddenly if peripheral circulatory collapse develops or a massive hemorrhage occurs

When the patient is first seen, he is usually dehydrated with a hot dry skin and a parched red tongue Patients, who are moderately or severely ill present a puffy appearance which may be generalized or may be limited to the periorbital region, the face or the extremities, it is due to edema, which is often difficult to detect early except by laboratory method (Fig 10) As the disease progresses, the edema becomes more widespread and more pronounced (Fig 6) Most of the time the edema does not pit and does not tend to settle in dependent areas In severely ill patients some degree of cyanosis usually will be seen

The neck often is slightly stiff, and Kernig's sign may be present The conjunctivae frequently are suffused early and the patient turns away from the light Severe prostration mental confusion dulling of the senses restlessness and hyperesthesia of the skin and muscles may be found early As prostration increases the patient becomes lethargic Muscular twitching fibrillary tremors and abnormal neurological signs such as ankle clonus or a positive Babinski reaction may appear

The spleen becomes palpable late in the first week of the disease and usually is firm and slightly tender The liver may be palpable but rarely is tender, jaundice may be seen occasionally but is not marked except in fatal cases Distention and constipation usually occur, although peristalsis is not abolished

Laboratory Examinations

The *hemoglobin* and *red blood cell count* usually show little change until the disease is far advanced when a normochromic, normocytic anemia will appear in most cases The low point is reached between the tenth and thirteenth days of rash and may precede or follow the clinical peak of the disease The hemoglobin may drop to 9 gm and the red blood cell count to 3 000 000 although a hemoglobin as low as 6 5 gm and a red cell count as low as 2 500 000 are not uncommon

The decrease in red cells probably is due to the debilitating effect of the disease it persists too long to be accounted for by an alteration in the distribution of the circulating blood The marked and rapid drop might suggest a hemolytic process but measurements of pigment in the blood do not support this thesis Destruction of erythrocytes by specific parasitization of red cells has not been demonstrated Extravasation of blood into the tissues and loss in the excreta have not been marked, though clinical tests for occult blood in the stool frequently are positive

In nearly all of the cases treated in the North Carolina Baptist Hospital the *white blood cell count* was below 10 000 in the first week of the disease Early leukopenia with total counts of 4 000 to 6 000 has been quite frequent in such cases a differential count shows a neutropenia As the disease progresses the white blood cell count frequently rises above 10 000 more often in the range of 13 000 Peaks above 20 000 or below 10 000 are relatively uncommon each occurring in about one fifth of the cases The highest count we have observed was 33 750 the lowest 3 350 When counts above 15 000 are seen usually they are in children[6]

As the disease progresses and leukocytosis develops an increase is noted in polymorphonuclear cells with a shift toward the left in the Schilling hemogram The young cells are mostly of the band or stab type toxic granulation of the polymorphonuclear cells is frequent In many cases the leukocytosis is associated with the appearance of secondary bacterial infection or follows hemorrhage The alterations in the total and differential white cell count are discussed further in subsequent paragraphs

The *urinalysis* at the onset usually shows no abnormality although *the urine volume may be reduced as a result of inadequate fluid intake* or decreased glomerular filtration pressure A trace of albumin consistent with the degree of dehydration may be present As the disease progresses slight albuminuria may appear possibly as the result of fever but it persists for only 2 or 3 days Albuminuria was not marked in any case in the Baptist Hospital series half of the patients had none at any time In 5 cases there was a 1 plus reaction for albumin and in _ the reaction was 2 plus or greater Occasionally the alterations of acute nephritis red cells and casts in the urine sediment are present in addition to albuminuria Five cases in our series of 46 cases showed small numbers of red cells to 5 per high power field in a centrifuged specimen for periods of 1 to 3 days Occasional hyaline and granular casts were seen in 8 cases

The *benzidine test for occult blood in the stool* frequently is positive occasionally gross bleeding or massive hemorrhage from the bowel may occur as a complication

The *cerebrospinal fluid* frequently will show alterations which reflect the clinical evidence of encephalitis although the changes cannot be correlated closely with objective neurological manifestations[10] In many instances the pressure is normal in other cases pressure as high as 300 mgm of spinal fluid are recorded Elevations in globulin as measured by

the Pandy reaction are rare Quantitative estimations of spinal fluid proteins showed an increase in 3 of 18 determinations, the maximum level observed was 265 mgm per 100 c c The spinal fluid protein composed chiefly of the smaller albumin molecule may indicate that the permeability of the cerebral capillaries to proteins is not markedly increased

The spinal fluid sugar usually is within the normal range 40 to 60 mgm per 100 c c The spinal fluid chlorides usually are in the range of high normal values 100 to 118 milliequivalents per liter (584 to 688 mgm per 100 c c) In almost every lumbar puncture in the Baptist Hospital series small numbers of red blood cells from 1 to 20 per cubic millimeter were found in the spinal fluid on taps performed without trauma The white blood cells predominantly small mononuclears were found increased in 5 instances numbering from 10 to 22 cells per cubic millimeter

For the first few days of the disease *blood chemical determinations* are most often within normal limits As the disease progresses, profound alterations in electrolyte balance and in protein metabolism usually occur[7, 10] The decreased intake of fluid and food and the increased sweating caused by fever are reflected by a drop in blood chlorides which may reach levels below 80 milliequivalents per liter (468 mgm per 100 c c) The carbon dioxide combining power usually is not greatly altered With dehydration and a decrease in the urinary output the nonprotein nitrogen rises occasionally exceeding 85 mgm per 100 c c When the urinary output becomes adequate the nonprotein nitrogen drops reaching normal levels by the time convalescence begins The level of the nonprotein nitrogen elevation cannot be correlated with the degree of protein destruction

The circulating blood proteins which usually are normal early in the course of the disease begin to drop during the first week and reach their lowest level late in the second week about the time the clinical peak occurs It is not uncommon for the total serum proteins to fall as low as 4 to 5 gm per 100 c c The serum albumin falls to a greater extent than the globulin fraction and frequently drops below 2 5 gm a level frequently said to be critical for the formation of edema In addition to the depletion of the tissue stores which is shown by the drop in circulating blood proteins a marked destruction of body proteins is reflected by the greatly increased excretion of nitrogen in the urine The equivalent of 3 to 6 gm of protein per kilogram of body weight may be recovered daily as urinary nitrogen

Increased *capillary fragility* usually can be demonstrated qualitatively by the application of a blood pressure cuff; it can be measured quantitatively by a simple suction technique utilizing glass syringes and a manometer.

The *blood platelets* are within normal limits and apparently are not responsible for the hemorrhagic phenomena.

The *prothrombin time* usually is normal early in the course of the disease, although it may become elevated later. Usually an abnormal prothrombin time will revert to normal following the administration of vitamin K. In one instance, however, the prothrombin time remained above minutes and 30 seconds for 5 days in spite of the daily parenteral injection of 4 mgm. of vitamin K; it reverted to normal with convalescence. The defect in prothrombin formation apparently is associated with liver damage.

Serial *liver function studies* have been performed on 16 patients in the Baptist Hospital series. The serum bilirubin, as measured by the van den Bergh test, was elevated in only one instance, a case in which other tests also showed evidence of extensive liver damage. In 5 cases a bromsulfalein test showed retention of the dye. The galactose tolerance test was within normal limits in all cases. The changes in the albumin-globulin ratio and prothrombin time already discussed may indicate some impairment in the synthesis of proteins. Alterations in the conjugation and excretion of hippuric acid were noted after oral or intravenous administration of sodium benzoate. This defect usually occurred during the third week, just after the clinical peak of the disease or in early convalescence. In all cases all hepatic functions returned to normal during late convalescence. A high protein diet will afford protection against liver damage.

Phenolsulfonphthalein excretion *tests of kidney function* usually fall within the range of normal. Urea clearance tests are usually normal, 70 per cent or better, or they may fall within the range of slight or questionable impairment of renal function with a clearane of 50 to 70 per cent. Occasional patients, 3 out of 16 in the Baptist Hospital series, show definite evidence of renal damage with a urea clearance of less than 50 per cent.

The *electrocardiogram* shows nonspecific changes in T waves which are similar to those found in myxedema, beriberi or edema of any kind. Prolongation of the P-R interval and other changes which can be confused with rheumatic fever have been observed infrequently. The changes usually revert to normal during convalescence.

Serial determinations of the circulating blood volume by the Evans blue technique reveal a normal blood volume, 3 400 c c of plasma for a man weighing 70 kg or 150 pounds, early in the disease A transient diminution is seen in severe cases at the clinical peak of the disease, i e between the twelfth and fourteenth days of rash with a return to normal during the period of lysis[18] The degree of alteration may be as much as 15 to 20 per cent of the control value In mild or moderately severe cases the blood volume may not be significantly altered Indeed where no defect in capillary permeability exists the blood volume actually may be increased if fluids are given to excess This situation is of more than academic interest since the plethora may overload the myocardium and set the stage for the precipitation of central circulatory (congestive) failure

Determinations of the extravascular fluid space following the injection of sodium thiocyanate show a gradual increase from the first week to a maximum at the clinical peak of the disease[18] The amount of fluid in the extravascular space may increase to almost twice the normal value of approximately 13 500 c c for a man weighing 70 kg (150 pounds) After the fever begins to subside the fluid is gradually mobilized and excreted and the thiocyanate space returns to normal during late convalescence (Figs 6 and 10)

The *levels of specific chemotherapeutic agents in the blood* should be followed when such agents have been administered The blood level of para aminobenzoic acid (PABA) can be determined by the techniques used for sulfonamides Because of the rapid excretion of the drug, blood should be drawn within 30 minutes after the administration of a dose Serum levels of antibiotics can be measured by biologic or spectrophotometric techniques but the accuracy of the determinations and the correlation of the blood levels with clinical response are not yet completely worked out

Bacteriological cultures of blood and sputum for the common gram positive cocci which secondarily invade the lungs should be made to determine the necessity for antibiotic therapy in the treatment of complications

Laboratory Examinations for Prognosis

In the Baptist Hospital series we were unable to predict the ultimate clinical severity of the disease or the outcome from either the *total*

or the *differential white blood cell count* Severe or fatal cases may show either a low or a high total count A marked rise in the total count frequently, but not always heralds the development of a complication

In the differential count the percentage of nonsegmented polymorphonuclears is usually highest near the clinical peak of the disease Reversal of the usual ratio between the segmented and nonsegmented forms is not common with recovery the nonsegmented forms return to low levels The most constant alteration is a rise in small lymphocytes concomitant with clinical recovery This rise occurs regardless of the total white blood cell counts throughout the course of the disease Indeed the rise may produce a relative neutropenia and lymphocyte counts of 60 to 70 per cent are encountered

Alterations in the percentage of monocytes are not remarkable though occasional patients will have a single count of 10 to 15 per cent Eosinophils usually tend to disappear during the acute phase of the disease and reappear with defervescence Counts above [illegible] per cent have not been seen in the absence of serum sickness The only fatal case in which eosinophils were present was that of a patient who died from a massive hemorrhage after the fever had begun to drop Basophils also tend to disappear during the acute phase of the disease they appear with surprising frequency in the range of 1 to 3 per cent during early convalescence

The *sedimentation rate* remains elevated and is of little aid in estimating the prognosis or detecting the development of complications

A delay in the appearance of *agglutinins* for proteus OX19 or of *complement fixing antibodies* is not sufficiently dependable evidence on which to base a poor prognosis Patients may exhibit clinical recovery before the immune titers have reached significant levels

On the whole clinical evaluation of the degree of toxicity the extent of the hemorrhagic phenomena and the amount of edema have been more helpful than any simple laboratory procedure in estimating the prognosis

Course

The clinical course varies from abortive and mild infections in which the patient may remain ambulatory to fulminating cases leading to death within 3 to 5 days In such instances the body defenses are overwhelmed by the toxemia of the infection In most fatal cases death occurs between the ninth and fifteenth days of rash patients rarely die after the four

teenth day. Near the peak of the disease the patient frequently becomes comatose, and neurological signs are more prominent.

Occasionally, after improvement has apparently begun, a recrudescence of symptoms will occur and a new crop of skin lesions will develop exactly as in typhoid fever; such recrudescences are not common, however.

Complications usually become evident by the time the disease reaches its peak in the middle of the second week of rash; they are discussed later under that heading. Convalescence is slow, and complete recovery may not take place for weeks, months or for as long as a year, even in a relatively mild infection. The sequelae are discussed under Prognosis.

The course of the disease in recently immunized individuals or those given suppressive chemotherapy may be atypical and often bizarre[1]. In these patients the usual time relationship between exposure and the appearance of signs and symptoms, the duration of the disease and the development of serological evidence of infection often are greatly altered. The multiple crops of skin lesions frequently seen and the irregular fever reflect the attempts by the parasite to break into the blood stream and to establish itself in new cells.

Complications

Circulatory Disturbances

Circulatory failure is most likely to occur between the eighth and fourteenth days of rash and may be peripheral or myocardial in origin. The mechanism by which peripheral circulatory failure develops and the principles for prophylaxis and treatment are discussed under Supportive Therapy.

Myocardial failure may result from the pathological process or from overloading the myocardium beyond its functional capacity by overzealous fluid administration. Impending myocardial failure can be recognized by a rise in pulse rate, the development of a gallop rhythm and an increase in venous pressure noted first in the neck veins and confirmed by direct measurement in the antecubital vein with a manometer.

The presence of a gallop rhythm or venous engorgement is an indication for digitalization. Digitalis should be administered with caution since a myocardium damaged by infection probably is more sensitive to

digitalis than one failing from purely mechanical reasons If the failure is sudden and is accompanied by pulmonary edema strophanthin or purified glycosides of digitalis should be given intravenously

Pneumonia

The most serious complication and the one which most frequently leads to death is pneumonia The pulmonary infection may be due to a true rickettsial invasion of the lungs in this type the sputum will be scanty and not purulent and the roentgenogram will show diffuse infiltration If this type of pneumonia develops irradiation over the lungs could be added to the specific therapy described above

More commonly pulmonary congestion occurs as a result of generalized interstitial edema Protein containing edema fluid furnishes an excellent culture medium for the bacteria ordinarily found in the mouth and may lead to pneumonia The full development of pneumonitis sometimes can be prevented by the administration of protein to control the edema and by frequent turning of the patient If the edema is on a cardiac basis the heart failure must be treated

Since penicillin is a relatively harmless drug it is probably wise to begin the immediate parenteral administration of 10 000 to 5 000 units of the aqueous solution every to 3 hours to patients who exhibit the slightest signs of pulmonary disease Aureomycin and possibly chloromycetin also are effective against most gram positive cocci the simultaneous administration of penicillin probably is not necessary when one of these drugs is being given If bacterial pneumonia develops under aureomycin or chloromycetin therapy or does not respond to penicillin it is most likely due to a gram negative rod and should be treated with streptomycin

Necrosis

Gangrene may develop in the distal phalanx of an extremity in any area of skin in the scrotum or in an ear lobe as the result of complete thrombosis of an artery where the collateral circulation is not adequate to prevent this The injection of procaine hydrochloride around the sympathetic ganglia may reduce the vascular spasm and improve circu

lation control the pain and prevent the aggravation of restlessness Spasmolytic drugs with generalized systemic effects, such as etamon and priscol should be used with caution in view of the already existing tendency toward low blood pressure Amputation or excision and skin grafting may be necessary if other measures fail, but usually can be postponed until early convalescence

DIAGNOSIS

Prodromal Period

The epidemiological history is the greatest help at this stage The onset and symptoms are similar to those seen in many other diseases, headache and backache are outstanding Before the rash develops diseases caused by the filtrable viruses must be especially considered—influenza measles encephalitis and poliomyelitis A lumbar puncture frequently will aid in the differential diagnosis since the number of white cells in the spinal fluid will be less than in encephalitis and poliomyelitis

Rash

The development of chills or chilly sensations suggests a blood stream invasion which is actually what occurs The disease at this stage must be differentiated from a septicemia of any other cause The headache and the hemorrhagic character of the rash, as well as the positive tourniquet test, make it very difficult to differentiate early spotted fever due to rickettsias from that due to meningococci In meningococcemia the rash frequently becomes purulent and necrotic in the center within 1 to 2 days bacteria can be stained in material aspirated from the lesions and can be cultured from the aspirate and from the blood

The rash in measles chicken pox and other similar exanthems may be suggestive of Rocky Mountain spotted fever at first but the rash of measles rarely becomes purpuric or confluent Measles usually appear first in the mucous membranes of the mouth whereas the rash of Rocky Mountain spotted fever is seen first in the skin of the extremities

The severity of the illness together with the mental clouding headache high fever and bradycardia may be suggestive of typhoid fever The rash in typhoid, however usually appears first on the abdomen continues to blanch on pressure for several days does not become so papular or petechial and maintains a paler rose color than is true for Rocky Mountain spotted fever

Endemic flea borne typhus occurs in the same general areas as spotted fever in the Southeastern states, however that disease usually is contracted in business establishments in urban areas during the cold months of the year Flea borne typhus is generally a much milder disease than Rocky Mountain spotted fever but may start with identical symptoms The rash usually appears first on the chest abdomen or back and spreads to the extremities it usually does not become so prominent nor so purpuric and frequently is fleeting

Errors in diagnosis usually occur in the clinically very mild infections or in the fulminating types

Laboratory Tests for Diagnosis

No test is available which will quickly establish the diagnosis early in the course of the disease A conclusive diagnosis can be made by recovery of the infecting organism from the patient The *infection test* is the most accurate method of proving the rickettsial etiology but the results cannot be obtained quickly enough to be of use in planning specific therapy

The rickettsias are found in the blood throughout the first and part of the second week disappearing when clinical improvement begins The parasitemia is heavy in severe cases but may be quite light in mild ones Male guinea pigs weighing about 400 to 500 gm can be infected by the intraperitoneal injection of 1 c c or more of whole blood transferred by syringe directly from the patient at the bedside [1] Citrated whole blood and ground blood clot can be used but are less desirable plasma and serum are not reliable If the infection is very mild or if the blood has been drawn late in the course of the disease *2 to 5 c c should* be used more than 5 c c of human blood may be toxic to the animal In fulminating cases blood removed from the heart within several hours after death usually will be infectious Blood shipped to a laboratory with several hours in transit may not give a positive reaction

The temperature of the pig should be taken daily by rectum and the scrotum examined for swelling reddening and necrosis If the reaction is positive fever appears in 2 to 6 days, rising for 4 to 5 days from the maximum normal temperature of 103 8 F (39 9° C) to 105 F (40 5 C) The severity of the disease in guinea pigs bears no relationship to the virulence of the strain for the patient In mild guinea pig infections a febrile reaction may be the only indication of illness, in severe cases the animals will die When there is a definite scrotal reaction experienced individuals can differentiate the gross lesions from those of endemic typhus with which they are often confused Smears from the tunica vaginalis should be made and will show rickettsias in most cases If more conclusive evidence is desired serological tests can be run on surviving animals or they may be given an immunity (protection) test by inoculation with a challenging dose of a Rocky Mountain spotted fever strain of rickettsias

Rickettsias isolated at autopsy from guinea pigs or human patients may be grown in fertile hens eggs by inoculation of the yolk sac with 0 5 to 1 0 c c of a suspension of ground infected tissue It is not yet established whether this technique is suitable for primary isolation of the organisms from whole blood

Although *blood cultures* performed by the usual bacteriological techniques will not grow the rickettsias blood should be taken for culture several times daily for 2 to 3 days when the patient is first seen Because simultaneous intercurrent disease such as tick-borne tularemia may occur the blood should be planted on special media containing cystine for *Pasteurella tularensis* and under increased carbon dioxide tension for *Neisseria meningitidis*

The most widely used confirmatory diagnostic procedure is the *agglutination test* employing a strain of proteus bacilli and the patient s serum (Weil Felix reaction) The test is not specific for Rocky Mountain spotted fever and does not differentiate between the various rickettsial infections On the whole however it is the most useful and practical test available although it may fail to confirm unusually mild infections or those in which there is an early fatal termination The OX19 strain of *Proteus vulgaris* usually is employed the patient s serum is serially diluted and its ability to clump a suspension of the organisms is observed

Agglutinins begin to appear during the peak of the disease or early in convalescence and the titer rises progressively Three blood samples should therefore be taken the first when the disease is suspected an

other during the second week and a third during late convalescence The first sample seldom is diagnostic and is used mainly as a control on the second and third A titer of 1 160 is highly suggestive but a titer of 1 320 is the lowest that can be considered definitely diagnostic A progressive rise during convalescence is as important as the final height of the titer

The reaction usually will disappear within a year though the titer may rise again with any subsequent infection which produces fever (anamnestic response) The reaction apparently depends on the presence of an antigen common to rickettsias and the proteus bacillus one antigen has been found to be a specific soluble substance probably a polysaccharide

The *complement fixation test* is a specific reaction for the spotted fever strain of rickettsias[3] The test becomes positive at about the same time as the proteus agglutination test A specimen of the patient s serum should be obtained as soon as the disease is suspected and another during convalescence several weeks after fever has subsided If the first specimen gives a negative reaction a titer of 1 16 or greater in the second is diagnostic Complement fixing antibodies will persist for at least 6 to 8 years The antigen is prepared from the yolk sac of infected hen s eggs and is commercially available the test is technically difficult and results are dependable only in experienced hands The test will be performed by the United States Public Health Service at the National Institute of Health Bethesda Maryland or at the Rocky Mountain Laboratory in Hamilton Montana

If the organism has not been isolated and serological confirmatory tests are inconclusive a *test of the protective power* of serum taken from the patient during convalescence can be carried out in guinea pigs Administration of 0 5 c c of the serum is carried out simultaneously with inoculation with a strain of Rocky Mountain spotted fever rickettsias carried in chick embryos or in other guinea pigs[12]

Theoretically it should be possible to make a diagnosis in the first few days of the infection by means of the soluble specific substance known to be produced by the rickettsias and presumably excreted in the urine This substance can be concentrated and utilized as antigen for precipitation tests or other immune reactions against convalescent serum from a patient or guinea pig known to have had spotted fever This technique is similar to that which has been used for typing of pneumococci

No diagnostic skin test has been devised and no diagnostic aid is given by the hematologic findings

The temperature of the pig should be taken daily by rectum and the scrotum examined for swelling, reddening and necrosis If the reaction is positive, fever appears in 2 to 6 days, rising for 4 to 5 days from the maximum normal temperature of 103 8° F (39 9 C) to 105° F (40 5 C) The severity of the disease in guinea pigs bears no relationship to the virulence of the strain for the patient In mild guinea pig infections a febrile reaction may be the only indication of illness, in severe cases the animals will die When there is a definite scrotal reaction, experienced individuals can differentiate the gross lesions from those of endemic typhus with which they are often confused Smears from the tunica vaginalis should be made and will show rickettsias in most cases If more conclusive evidence is desired serological tests can be run on surviving animals or they may be given an immunity (protection) test by inoculation with a challenging dose of a Rocky Mountain spotted fever strain of rickettsias

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prevent 8 deaths a mortality of 17 per cent during the same year, however 9 deaths occurred in 341 cases throughout North Carolina a mortality of 2.7 per cent Because of the discrepancy in the size of the groups the difference may not be statistically significant but it has been our clinical impression that vigorous supportive therapy has saved individual patients who would otherwise have died and that in other cases the degree of toxemia has been decreased and convalescence shortened

In Topping's experience with 5[illegible] serum treated cases the initiation of antiserum therapy before the third day of rash has resulted in a reduction of mortality from the expected figure of approximately 19 per cent [illegible] The initiation of immune serum therapy after the third day of rash has not altered the ultimate prognosis, though it may make the patient less toxemic

The results of treatment with para aminobenzoic acid (PABA) are difficult to evaluate from the reports in the literature[illegible] Many of the cases were treated in the second week of the disease and improvement began at about the time it would have been expected in the natural course of the disease In cases treated with PABA within the first week of the disease the prognosis is fair to good and is better than with supportive therapy alone after the first week of the disease PABA probably has little effect on the ultimate prognosis

Aureomycin and chloromycetin on the other hand appear to be definitely superior to any other therapeutic agents previously tried The prognosis becomes good in any except the most severe cases if treatment is started in the first week of the disease Late treatment in the second week improves the prognosis over that expected with supportive therapy and probably with PABA Experience with the drugs is too limited however to justify an attempt to estimate the prognosis in percentages

The duration of convalescence is definitely decreased by supportive therapy it is shortened still more by early treatment with PABA and is decreased most by aureomycin and chloromycetin therapy Because of the wide variation in the severity of individual cases it is difficult to estimate the shortening in terms of days

In Reinfections

Recovery from Rocky Mountain spotted fever confers a considerable degree of immunity which apparently is lifelong Immunity is not complete however for second and third cases have been reported In

Prognosis and Mortality

In Untreated Cases

In untreated cases the overall mortality for the United States as a whole has been about 23 per cent for the years 1939 through 1946 The mortality will be altered by the virulence of the local strain As a general rule the prognosis becomes increasingly poor with advancing age, the disease is especially severe in individuals past 40 years of age Topping has calculated the average mortality rate for patients under 40 as approximately 13 per cent and for patients above that age as about 41 per cent[4]

Vaccination within the year in which the infection is acquired improves the prognosis tremendously The mortality in individuals, who are infected with Rocky Mountain spotted fever in the same year that they were vaccinated has been estimated by Parker at 9 per cent as compared with 76 per cent in unvaccinated individuals in a comparable area[1] In addition to reducing the mortality recent immunization decreases the clinical severity of the disease and its duration

It is difficult to estimate the ultimate prognosis from the appearance of the patient at the time he is first seen The greater the clinical severity of the disease the poorer the prognosis We have classified cases as mild if the tourniquet test is negative throughout the illness if edema is minimal or absent and if the pulse and blood pressure remain stable Moderate cases are those in which the patient exhibits a positive tourniquet test slight clinical edema tachycardia and toxic symptoms The disease is considered severe if marked purpura moderate to marked clinical edema delirium and other signs of severe infection are present In our experience the temperature peak and the total or differential white blood cell count have been of no help in estimating prognosis Complications especially pneumonia make the prognosis poorer

In Treated Cases

Complications are decreased and the prognosis improved by specific and supportive therapy The time in the course of the disease at which therapy is instituted will affect the prognosis If supportive therapy alone is given early treatment will decrease the number of complications and the extent of the physiological disturbance Vigorous supportive therapy in the North Carolina Baptist Hospital series of 46 cases did not

lowed from the onset If specific therapy can be given early the duration of the illness will be shortened Antibiotic therapy often induces a rapid and dramatic reduction in the severity of the clinical picture, when prompt recovery is initiated within a few days after appearance of the rash, subsequent treatment will be that of any acute infectious disease of short duration

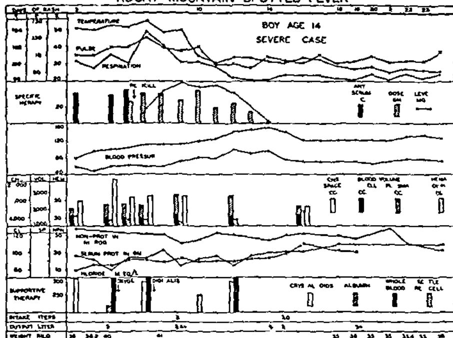


Fig 11 Summary of the clinical course laboratory findings and supportive and specific therapy in a severely ill 14 year old boy The rash and edema are illustrated in Fig 6

(This chart was first reproduced in the *American Practitioner* April 1947)

Antibiotic Therapy — The recent development of antibiotics of high antirickettsial activity is revolutionizing the treatment of Rocky Mountain spotted fever Penicillin is moderately effective against rickettsias in eggs but in animals it appears to have little or no effect Streptomycin has proven of no value *Aureomycin*, an antibiotic of the same general family as streptomycin gives promise of developing into a very useful drug for therapy in rickettsial spotted fever[6] In chick embryos aureo

human beings and guinea pigs treated with PABA antibody formation has not been depressed to an extent that would seem to make reinfection more likely. It is quite possible that early treatment with aureomycin or chloromycetin may suppress the antigenic stimulus and hence the immune response so greatly that reinfection would occur almost as readily in patients who have recovered as in individuals who have never been infected. The protection should be about comparable to that conferred by vaccination the same number of years before.

Recovery from rickettsial spotted fever does not confer cross immunity against endemic flea borne typhus or other infections with rickettsias that occur in this country. A minimal increase in resistance to other rickettsial diseases as a group can be demonstrated immunologically by proteus agglutinations and in some instances by cross reactions in low titer to complement fixation tests using other strains of rickettsias as antigen. The degree of possible protection is of little clinical significance, however.

Treatment

Specific Therapy

Rocky Mountain spotted fever presents an extremely difficult therapeutic problem (Fig. 11). Until the diagnosis is definitely established by the appearance of the rash therapy should be expectant. The prophylactic administration of specific serotherapy and chemotherapy after tick bite and before the development of clinical signs has not yet been shown to be effective. Specific therapy is most efficacious if it can be started at the earliest sign of rash; its value is progressively diminished after the first week of the disease.

Since the rickettsias are located intranuclearly, the ideal therapeutic agent should be able to penetrate two cell membranes of the parasitized host cells. An agent which could be administered prophylactically after a history of tick bite in an endemic area or early in the course of the disease before the rash is fully established during the stage of heavy parasitemia would not have to penetrate cells. As yet no therapeutic agent has been developed which is completely effective in all stages of the disease.

Since the physiological effects of the infection are so severe, the principles of supportive therapy discussed in detail later should be fol-

tiveness of aureomycin against the usual secondary invaders which commonly cause fatal bacterial pneumonia simultaneous administration of any other antibiotic such as penicillin should not be necessary In our experience to date complications have been less numerous than with any other type of therapy Large loose stools are noted whether the drug is given orally or parenterally With some lots of the drug nausea or vomiting has been noted requiring a simultaneous hypodermic injection of atropine with each dose

Since aureomycin has so far seemed to be of low toxicity, it apparently would be safe to institute therapy on suspicion of rickettsial spotted fever Time is of the greatest importance in preventing severe complications of the disease and it is apparently safer to administer the drug erroneously to a patient suspected of having the disease than to allow a full blown case to develop

Chloromycetin, another antibiotic similar to aureomycin apparently has proven effective also in the treatment of Rocky Mountain spotted fever It too is well absorbed from the gastrointestinal tract and is apparently of low toxicity Vomiting has been encountered but no diarrhea has yet been reported It is furnished in the form of tablets containing 0 5 gm The drug has a bitter taste which can be disguised by pulverizing tablets and suspending them in a sweetened vehicle or the drug can be placed in a gelatine capsule

The proper dosage of the drug the schedule of administration and the duration of treatment are yet to be determined The initial dose employed at this writing is 75 mgm per kilogram of estimated body weight administered in or 3 parts at intervals of approximately 1 hour After the initial dose the drug is given at 3 hour intervals day and night in doses of 0 25 gm for children and 0 5 gm for patients above 16 years of age

The inoculation of guinea pigs with blood from patients treated with the drug suggests that the parasitemia disappears by the second day of treatment In all cases reported up to this time, therapy with chloromycetin irrespective of the height of the preceding fever the age of the patient or the stage of the disease has been followed by a fall of temperature to normal levels within 76 hours after the initial dose the average duration of fever has been between and 3 days A much larger experience with the use of this antibiotic is necessary to demonstrate whether a brief course of treatment is adequate to eliminate completely the rickettsial infection No recurrences or recrudescences have been observed to date, however

mycin is highly effective against most strains of rickettsias It is still more active in guinea pigs even if it is given late in the course of the infection Aureomycin apparently has the property of penetrating cell membranes and attacking rickettsias within cells

The drug appears to be relatively nontoxic and can be given parenterally or orally It is supplied in capsules of 250 mgm for oral administration and in ampules containing 50 mgm of the lyophilized drug as the hydrochloride for parenteral injection The best method of administration and the optimal dosage are yet to be completely worked out At this writing the daily oral dose seems to be 50 to 100 mgm per kilogram 3 to 6 gm daily for an adult given on a 4 to 6 hour schedule Since alkalis very rapidly inactivate the drug none should be administered by mouth for at least 2 hours after an oral dose of aureomycin

The parenteral dose of aureomycin probably should be in the range of 5 to 10 mgm per kilogram per day The drug is unstable in solution If maximum potency is to be assured buffered aureomycin should be prepared freshly from the powdered drug for each parenteral dose Parenteral injections are somewhat painful since the drug is buffered on the acid side The discomfort can be reduced without loss in potency by the addition of 0 5 c c of a solution of 1 per cent procaine to each parenteral dose

Aureomycin is excreted slowly through the kidney and appreciable blood levels can be detected for 6 hours after a single injection Serum levels can be determined by an assay method, which employs a spectrophotometer to measure the growth of a standard strain of staphylococci known to be inhibited by the drug[6] Since the drug apparently is rickettsiostatic and acts by reducing the number of organisms in the body to a point where a low degree of immunity is clinically effective, administration should be continued for 2 to 3 days after the temperature is normal

In severe cases treated early in the course of the disease a fall in temperature has been noted within 2 to 3 days (Fig 9) The patient becomes less toxemic as the fever subsides and the rash begins to fade The clinical response in extremely ill patients treated late in the course of the disease is not so dramatic as in those treated earlier but still is superior to that obtained with any other treatment previously tried

Aureomycin is easier to administer than para aminobenzoic acid (PABA), the 6 hour schedule is much more convenient and no difficulty is encountered in giving the drug through a duodenal tube if the patient is being fed by gavage In view of the laboratory evidence of the effec

when the drug is given late in the course of the disease i e after the seventh day of rash

For children PABA should be given in a dose of 1 to 2 gm per kilogram of body weight daily Small children should receive the higher dose large children the lower dose and children of intermediate size a dosage in between the two The daily dose should be divided into equal portions administered on a hour schedule day and night For adults of average size 150 pounds the initial therapeutic dose is 4 to 6 gm followed by doses of to 3 gm every hours It is probably wise to restrict the total daily dosage in an adult to a maximum of 30 gm daily for a period of not more than one week

Blood levels of 30 to 50 mgm per 100 c c should be attained in some instances a level of 60 mgm per 100 c c may be necessary to obtain a favorable response If definite improvement is not noted within 48 hours the dose should be increased to a point which will produce a blood concentration approaching but not exceeding 60 mgm per 100 c c The blood concentration may build up if the urinary output is restricted

The powdered drug is flocculent and does not dissolve readily in ordinary liquids When suspended in water and administered through a stomach tube it tends to clog up the lumen The acid is available in tablets of 0 5 gm but these must be crushed and administered by tube to comatose or severely ill patients Since the drug is a weak acid its administration in a chilled 5 per cent solution of sodium bicarbonate (10 c c per gram of PABA) has been recommended especially in children where an inherent tendency toward acidosis exists The powder is more soluble in an alkaline medium it is more palatable if suspended in fruit juice which in itself has some alkalinizing power The acid cannot be given parenterally

Tablets containing 0 5 gm of the sodium salt of PABA are available also The salt is much more soluble than the acid and its use makes it unnecessary to administer alkalies simultaneously However the amount of sodium contained may be sufficient to precipitate edema or to increase any which may already be present It should be given in the same dose as the acid Ampules containing 5 c c of a 0 per cent solution or 100 c c of a 10 per cent solution have been prepared for intravenous administration to comatose patients Vials containing or 5 gm of the powdered salt have been furnished us for preparation of an intravenous solution or for use with a gavage tube

When PABA in either form is given the carbon dioxide combining power of the blood should be checked frequently Since the drug has a

The relative effectiveness of aureomycin and chloromycetin has not yet been determined in alternate cases. Chloromycetin has been synthesized and the synthetic drug may be available in larger quantity and may prove to be cheaper than the natural product.

There is some evidence that the administration of an antibiotic such as aureomycin early in the course of a rickettsial infection may suppress or delay the antibody response as measured by the complement fixation reaction. This retardation or suppression of immunity probably can be explained by the fact that the reduction in the number of infecting organisms early in the course of the disease provides inadequate antigenic stimulation. It may therefore be difficult to confirm the diagnosis by serological methods and protection against subsequent reinfection may be much less than after a full febrile course.

The decrease in the period of prostration and convalescence before resumption of normal activities tends to offset the current high cost of therapy with these antibiotics. It may be found that a combination of aureomycin or chloromycetin with PABA will be even more effective than either drug alone.

Chemotherapy. — The goal of chemotherapy is the development of a rickettsiocidal drug. *Heavy metals* (arsenic and mercury) have been given but the results are not dramatic.*

All sulfonamides are definitely contraindicated throughout the course of the disease, since their administration to human beings as well as to experimental animals has increased the severity of the illness.

Discovery of the harmful effects of the sulfonamides in Rocky Mountain spotted fever led to the clinical trial of *para aminobenzoic acid (PABA)*, one of the B complex vitamins, which is antagonistic to the sulfonamides in the test tube. PABA inhibits the growth of rickettsias in vivo but a very large amount of the drug is required. The drug apparently activates an enzyme necessary for growth and accelerates cell metabolism by increasing respiration. As a result, the rickettsias suffer in the competition with the host cells and multiplication of the organism is thought to be hindered. The drug has been found to inhibit the growth of the organism in chick embryos and to be effective therapeutically in guinea pigs infected with Rocky Mountain spotted fever.

If aureomycin or chloromycetin is not available, PABA should be administered. In most of the reported cases where treatment with PABA was begun early in the course of the disease a beneficial effect has been noted within 48 to 96 hours (Fig. 9). The effect is much less dramatic

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For children PABA should be given in a dose of 1 to gm per kilo gram of body weight daily Small children should receive the higher dose large children the lower dose and children of intermediate size a dosage in between the two The daily dose should be divided into 12 equal portions administered on a 2 hour schedule day and night For adults of average size 150 pounds the initial therapeutic dose is 4 to 6 gm followed by doses of to 3 gm every 2 hours It is probably wise to restrict the total daily dosage in an adult to a maximum of 30 gm daily for a period of not more than one week

Blood levels of 30 to 50 mgm per 100 c c should be attained in some instances a level of 60 mgm per 100 c c may be necessary to obtain a favorable response If definite improvement is not noted within 48 hours the dose should be increased to a point which will produce a blood concentration approaching but not exceeding 60 mgm per 100 c c The blood concentration may build up if the urinary output is restricted

The powdered drug is flocculent and does not dissolve readily in ordinary liquids When suspended in water and administered through a stomach tube it tends to clog up the lumen The acid is available in tablets of 0 5 gm but these must be crushed and administered by tube to comatose or severely ill patients Since the drug is a weak acid its administration in a chilled 5 per cent solution of sodium bicarbonate (10 c c per gram of PABA) has been recommended especially in children where an inherent tendency toward acidosis exists The powder is more soluble in an alkaline medium it is more palatable if suspended in fruit juice which in itself has some alkalinizing power The acid cannot be given parenterally

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When PABA in either form is given the carbon dioxide combining power of the blood should be checked frequently Since the drug has a

tendency to produce mild leukopenia the total white blood cell count should be determined daily during its administration PABA may cause abdominal distention delirium and other toxic symptoms which usually disappear quickly on withdrawal of the drug

The administration of the drug should be continued for several days after the temperature has returned to normal The optimum duration of therapy is not yet known it is possible that the drug should be continued for the duration of the expected febrile period i e through the fourteenth day of rash the 2 hour schedule should be maintained though the dose may be reduced

PABA probably has some effect on the host as well as on the parasite, its chemical structure is related to that of salicylates which are known to exert their therapeutic action on affected tissue If the drug does increase cell metabolism the principles of supportive therapy outlined later must be followed even more closely

The administration of PABA suppresses the development of fever and scrotal reaction in infected experimental animals rickettsias appear in the circulating blood at the same time as in untreated animals[30] Immunity is not affected since complement fixing antibodies appear in treated and untreated animals at the same time and the rise in titer during convalescence is similar in both groups

Serotherapy — An effective hyperimmune rabbit antiserum processed to concentrate the immune bodies in the globulin fraction is commercially available Full therapeutic doses of serum given soon after the rash appears usually lessen the clinical severity of the disease and reduce the toxemic symptoms though the beneficial effects are somewhat transient The recommended dose is 1 c c per kilogram of normal body weight It is intended for intramuscular administration though it can safely be given intravenously In our experience with the serum best results have been obtained when this dose is repeated daily for 3 days and when the initial dose is given before the third day of rash if begun after this time serum therapy causes little if any clinical improvement[3]

In some instances the rash is markedly altered by serum therapy, this alteration may indicate a lessening of the vascular damage (Fig 8) On theoretical grounds one would expect that the serum might prevent vascular damage and leakage of protein into tissue spaces In our limited experience serum treated patients have had less edema than patients treated with supportive therapy alone The administration of antiserum however does not prevent alterations in the total serum proteins and the albumin globulin ratio

Though the processing of the serum reduces the number of allergic reactions a skin test or a conjunctival test for hypersensitivity should be given before it is administered Serum sickness may develop in the second week after injection and produce urticaria joint pains and a rise in fever accompanied by eosinophilia The discomfort can be reduced by aspirin given orally and epinephrine injected subcutaneously in some instances antihistaminics by mouth or the intravenous administration of a 1 per cent solution of procaine is effective in relieving the symptoms

The development of potent antibiotics such as those discussed in preceding paragraphs may relegate serum therapy to use only in extremely toxemic patients or in those who have an idiosyncrasy to chemotherapeutic agents

Supportive Therapy

In uncomplicated cases diet and good nursing care are the most important factors in supportive therapy which is directed at the maintenance of nutrition and the prevention of cardiovascular complications and pneumonia The patients who are dehydrated at the time they are first seen especially those who have elevated blood levels of nonprotein nitrogen or low blood chloride levels should be given calculated amounts of an isotonic solution of sodium chloride until the urinary flow returns to normal Those patients who have nitrogen retention but normal blood chlorides should be given a 5 per cent solution of dextrose in water If the carbon dioxide combining power is low sixth molar sodium lactate solution should be administered The fluids may be given intravenously or subcutaneously but no single injection should contain more than 20 c c of fluid per kilogram of body weight If fluids can be taken orally the same effect can be achieved with less danger of precipitating pulmonary edema

Because of the alterations in protein metabolism the intake of proteins should be increased as soon as the disease is suspected in order to prevent the development of a full blown protein deficiency Any type of nutritious food in easily digested form is satisfactory The daily diet should contain 4 to 6 gm of protein per kilogram of normal body weight, depending on the age of the patient and the clinical severity of the disease Because damage to the liver occurs in moderately severe or severe cases the diet also should be low in fat and high in carbohydrate Unless an adequate caloric intake is maintained marked muscular wasting with loss

in weight occurs as the disease progresses The loss of flesh usually is masked by the generalized interstitial edema during the acute phase but becomes evident during convalescence Even children, whose metabolism is normally higher than that of adults will not only maintain their weight but may actually gain weight during the illness, if supportive diet therapy is adequate

In the first few days of illness the patient will take food and fluid by mouth If he becomes delirious comatose or uncooperative and the desired intake is not attained the diet should be supplemented or replaced by liquid feedings with a high protein content Most children are unable to take the amount and type of food required and should receive gavage feeding as soon as they refuse the diet This procedure tires the patient less than prolonged attempts to feed him a general diet and saves nursing time If necessary either adults or children can be maintained for days with gavage feedings given every 2 hours through a large caliber nasal tube left constantly in the duodenum

A formulua which has proved satisfactory is as follows skimmed milk 850 c c powdered milk 100 gm corn syrup 75 gm , concentrated fish oil to furnish 800 units of vitamin D and 2,500 units of vitamin A, niacinamide 25 mgm , ascorbic acid 150 mgm , thiamin chloride 5 mgm , riboflavin 5 mgm , menadione 1 mgm or a water soluble synthetic equivalent 4 mgm This amount contains 115 gm of protein negligible fat, 118 gm of carbohydrate 932 calories (0 9 per cubic centimeter) and adequate vitamins If the caloric intake must be increased substitution of whole milk for the skimmed milk will add 34 gm of fat the formula will then contain 1, 38 calories (1 2 per cubic centimeter) The mixture thickens upon refrigeration and should be warmed to body temperature before administration It has a consistency and flavor similar to malted milk , the addition of chocolate syrup makes it sufficiently palatable to be drunk from a cup The administration of protein hydrolysates in our experience has been of no additional value

When gavage feedings are used the tube should be washed out with water after each administration of food or medicine It is wise to change the tube from one nostril to the other at least every 48 hours the nose and pharynx should be rested several hours before reinsertion

The intake of all vitamins should be increased Vitamins A B_1 C and K should be given in full therapeutic doses because of their possible effect on infection shock capillary fragility and the bleeding tendency respectively Niacin should be given in the form of the amide since niacin itself (nicotinic acid) may not be methylated in the presence of

liver damage The excretion of vitamins has been found to be increased in Rocky Mountain spotted fever in fact the breakdown products of nicotinic acid have been excreted in larger quantities in spotted fever than in any other infectious disease observed in our hospital[31]

As the disease progresses alterations in capillary permeability become evident The degree of disturbance observed in the blood chemical findings especially in the nonprotein nitrogen and chloride values, requires attention The administration of glucose and saline will cause the blood chemical values to return to normal but the altered capillary permeability permits plasma to be washed out[2] The circulating plasma protein thus may be reduced sufficiently to alter osmotic equilibrium further and to allow more crystalloids to remain outside the blood vessels This vicious cycle leads to peripheral circulatory collapse (medical shock) The serum proteins drop precipitously in such instances the circulating blood volume is decreased and the available fluid space increased

If the plasma proteins are found to be low or falling rapidly or if an appreciable drop in systolic and diastolic blood pressures gives evidence of impending circulatory collapse preformed proteins should be administered Intravenous replacement therapy in the form of purified albumin plasma or whole blood increases the intravascular osmotic pressure enough to allow crystalloids to be given safely Not all the replaced protein will be retained in the blood stream but some crystalloids will be reabsorbed into the blood vessels on the venous side A very large amount of preformed protein may be required to restore the circulating blood volume and blood constituents to normal We have administered as much as 2 800 c c of whole blood and plasma in a period of 10 days to a 2 year old child weighing 11 7 Kg and 2 500 c c of plasma in 36 hours to a 15 year old boy

Concentrated serum albumin 25 gm per 100 c c is a very powerful osmotic agent and can increase the blood volume 14 c c for each gram administered This degree of response is not usually attained in Rocky Mountain fever however The advantage of albumin lies in its small bulk and low salt content though its mode of action is the same as that of the more widely available plasma The high protein diet described above if administered early in the illness will reduce the amount of preformed protein necessary for support of the circulation

If the hemoglobin or hematocrit indicates a reduction in red cells whole blood would be preferred to plasma or albumin If the serum proteins have been maintained by feeding and anemia is still present or

if a gallop rhythm venous distention or other signs of myocardial failure are present settled red cells will increase the oxygen-carrying capacity of the blood and help to overcome anoxia without overloading the circulation the blood volume is not increased as much by the administration of cells alone as by the use of whole blood

The type and quantity of parenteral therapy given should be governed by clinical judgment and by careful laboratory control The efficacy of supportive treatment should be checked by repeated laboratory determinations to be certain that the desired results are being obtained In severely ill patients for instance the total serum proteins may have to be determined at intervals of 3 to 8 hours during the critical period It is possible to overload the circulation in comatose individuals by unwisely chosen fluid therapy administered in excessive quantities through an indwelling duodenal tube

Because of the possibility of myocardial damage, the quantity and speed of administration of parenteral fluids should be governed carefully to avoid overloading the circulation and precipitating acute central (myocardial) circulatory failure and pulmonary edema, this danger is greater if albumin is used

Oxygen therapy should be given by a nasal tube facial mask or oxygen tent as soon as impending circulatory failure pneumonia or myocardial failure is suspected If the administration of oxygen is withheld until cyanosis is deep and the indications obvious, irreparable damage may have been done

In view of the possibility that the defect in capillary permeability is due to the effect of an antigen antibody reaction the administration of antihistaminic agents during the first and second weeks of rash might be helpful

Severe headache extreme restlessness or increasing drowsiness due to an elevated spinal fluid pressure may be quickly improved by reducing the pressure halfway to the normal level the puncture should be repeated the following day if necessary If the optic disc margins are markedly blurred cisternal puncture would be a safer procedure Hiccup which is probably due to irritation of the central nervous system resulting from vascular injury may prove extremely resistant to therapy Heavy sedation with barbiturates scopolamine or other drugs may be necessary Herpes simplex may be troublesome but rarely is *dangerous*

In the long run the patient must still cure himself No supportive therapy will be helpful unless the patient s immune response can conquer the organism and his powers of repair are capable of overcoming the

vascular defect If in doubt it is probably better to undertreat than to overtreat the patient

Nursing Care

Nursing care should be directed toward protection of the skin prevention of pneumonia resulting from inadequate aeration of the lungs and maintenance of nutrition Necrosis of the skin may occur over the pressure points in comatose patients or may develop in areas of severe hemorrhagic rash meticulous constant gentle and painstaking care must be given to the skin to prevent breaks through which secondary bacterial invaders can enter or the development of decubitus ulcers Frequent turning of the patient and the use of a rubber ring will help to prevent the latter complication turning will also delay the development of hypostatic pneumonia

Diet and feeding have been discussed under supportive therapy If the patient has no oral feedings or is comatose the danger of parotitis should be combatted by swabbing the gums several times daily with the juice of half a lemon in an ounce of glycerine or mineral oil

Occasionally as the result of damage to the central nervous system the patient may sleep with his eyes open Instillation of some mild protective non evaporating substance such as cod liver oil will prevent drying out of the cornea and the development of corneal ulcers

Isolation

Since the disease is of low infectivity to human beings except through the medium of the tick strict isolation is not necessary The patient on admission should be carefully searched for ticks so that they cannot transfer to the nurse or physician The blood of the patient early in the course of the disease is *infectious if accidentally inoculated under the* skin through a needle prick Even gangrenous skin lesions however are not dangerous to another individual and rubber gloves are not necessary to prevent transmission of rickettsias Gowns are not necessary A mask worn by the nurse may prevent the transfer of secondary bacterial invaders to the respiratory tract of the patient

Prevention

Personal Measures

Control of the infection in nature is not feasible The greatest protection to an individual lies in preventing the attachment of a tick to the skin or in removing it before the rickettsias have become activated Ticks usually transfer from vegetation to the clothing at a height of 18 inches or less from the ground, then they will crawl up the clothing and at the first opening in it approach the skin High boots, leggings, puttees or socks worn outside the trousers will hinder the tick from attaching itself to the leg or crawling up it If there are no openings in the clothing at the ankle belt line or shirt front, the tick will continue, over the space of several hours to crawl up the clothing, attaching itself at a favorite spot on the neck It is wise, therefore in tick infested country to pass the hand frequently over the back of the neck and behind the ears Any tick observed on the clothing should be removed at once before it has a chance to reach the body[1]

Once on the skin ticks seldom attach themselves immediately, after becoming attached they rarely transfer the infection until they have fed for several hours It is usually sufficient, therefore, to inspect the body and clothing twice daily when in tick infested country All clothing should be removed in the search for ticks, clothing should not be laid on the ground since ticks may crawl onto it Ticks transfer from dogs to children with ease The children should be stripped before the midday nap and when coming in from play for the evening meal, a thorough inspection of the skin and hair should be made

If a tick is found attached to the skin it should be removed immediately and as gently as possible so as not to squeeze feces out of the insect It is desirable to detach the tick by slipping small forceps or a hypodermic needle under the mouth parts and lifting it off If the tick is pulled off with the fingers it would be advisable to handle it with a small piece of paper The small wound caused when the mouth parts and the tiny piece of attached skin come out with the insect should not be traumatized by scratching or squeezing since tick feces may be accidentally inoculated into the raw area The abrasion should be touched with any available disinfectant such as iodine or a mercurial antiseptic or simply be washed with soap and water

Attempts are being made to develop a tick repellent which can be placed on the body or impregnated in the clothing no completely satis

factory agent has yet been found although some give promise[33] The ordinary mosquito repellents are ineffective No material is known which can be fed to dogs or other animals to repel ticks or to prevent them from becoming attached

Vaccination and Other Specific Measures

Vaccines which have definite protective value are available The degree and duration of protection vary with the immune response of the individual vaccinated the period of effective immunity is less than a year however Even more important factors in determining infection of an individual are the virulence of the infecting strain of rickettsia and the size of the inoculum transferred from the tick The original vaccine was prepared at the Rocky Mountain Laboratory of the National Institute of Health from the tissues of infected wood ticks[1] This vaccine gives effective protection but also produces many local and occasional severe systemic reactions A more satisfactory vaccine has been prepared from rickettsias grown in the yolk sacs of fertile hens eggs The reactions to this type of vaccine are much less frequent and severe than with that prepared from ticks The immunizing power of the two types of vaccine is comparable

Either vaccine should be injected subcutaneously or intramuscularly in 3 doses of 1 c c each or doses of 2 c c each given 5 to 7 days apart In allergic individuals it is wise to give an intradermal skin test before administering the first dose of vaccine A full course of vaccine should be given each season in the late winter and early spring approximately one month before ticks are expected to appear It is doubtful whether immunization is of any value after a tick bite has occurred

In the West individuals who are living in highly endemic areas or in localities where the strain is of great virulence and individuals whose occupation takes them into such areas should be vaccinated regularly Tourists or vacationists should be vaccinated if their trip to endemic areas will expose them to ticks In the East it is doubtful whether all children should be immunized Children in counties where the disease is most prevalent (these counties can be determined by spot maps obtained from the various state health departments) might well be immunized yearly until the age of 15 The administration of the vaccine to adults who hunt or fish frequently or who take regular camping and hiking trips in the country is worth while

The effectiveness of the vaccine has been demonstrated by Parker[11] Over a period of several years in western Montana there were 38 deaths in 50 non vaccinated adults a case fatality rate of 76 per cent, and only 3 deaths in 49 persons, who had been vaccinated within the same year, a mortality of 9 per cent It can be seen that the immunization did not prevent clinical infection in some people, but that the disease was much less severe in vaccinated individuals Protection usually is adequate to prevent clinical disease resulting from infections with the relatively mild strains of spotted fever against the highly fatal type children are more fully protected than adults However previous immunization may mean the difference between life and death if an infection is acquired

Whether immune antiserum would be of value prophylactically after exposure is unknown Chemotherapy administered prophylactically or after exposure has not yet been shown to be effective It is not likely that para-aminobenzoic acid (PABA) would be effective in completely preventing the disease Aureomycin or chloromycetin two antibiotics which have been discussed in more detail in the section on treatment may be found to have suppressive properties Since no method is available for differentiating between infected and non infected ticks the drugs would have to be taken regularly while the individual was in an endemic area This procedure is impractical for persons living in such a locality but might be used for periods of a few days by vacationists Unless the administration of the drugs is continued for 3 weeks after the exposure is terminated withdrawal may be followed by a delayed atypical form of the disease

Community Measures

The clearing of brush weeds and other vegetation around houses or cabins has some limited value since it removes from the immediate vicinity shelter for the vector and animal reservoir Spraying an area with DDT or other insecticides is impractical because of the huge territory which would have to be covered and the difficulty in getting under low vegetation Furthermore the procedure has not yet been proved to be completely effective[11]

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The effectiveness of the vaccine has been demonstrated by Parker[1] Over a period of several years in western Montana there were 38 deaths in 50 non vaccinated adults a case fatality rate of 76 per cent, and only 3 deaths in 59 persons, who had been vaccinated within the same year, a *mortality of 9 per cent It can be seen that the immunization did not* prevent clinical infection in some people, but that the disease was much less severe in vaccinated individuals Protection usually is adequate to prevent clinical disease resulting from infections with the relatively mild strains of spotted fever against the highly fatal type children are more fully protected than adults However, previous immunization may mean the difference between life and death if an infection is acquired

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Community Measures

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CHAPTER XVII-A

TSUTSUGAMUSHI DISEASE

By ANDREW WATSON SELLARDS

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INTRODUCTION

Synonyms — Akamushi disease Kedani disease Japanese flood river fever

Definition — Tsutsugamushi disease is an acute self limited infection transmitted by the mite *Trombicula akamushi* and accompanied by a maculo papular eruption The disease conforms very closely to the symptom complex presented by typhus and Rocky Mountain spotted fever

GEOGRAPHICAL DISTRIBUTION

The distribution of tsutsugamushi disease is curiously limited Characteristic severe cases occur on the western coast of the island of Honshu the principal island of the Japanese archipelago and especially in the prefectures of Niigata and Akita The disease in a somewhat milder form is found also in the island of Formosa In Sumatra and in the Federated Malay States a still

The gravid female (in length about 1 mm) lays her eggs in the soil The resulting larvae seek some mammal in Japan the vole to obtain a blood meal for continuing their development The larva (about 250 to 300 μ in length) is the only stage in development in which the mite sucks blood Voles when inoculated with tsutsugamushi virus develop no symptoms but they carry the virus for variable periods of time and can pass it on to uninfected mites After three or four days the larva drops off from its host and returns to the soil The development continues to the nymph and adult which are free living forms that feed for example on plant juices The entire cycle of development probably takes place in about 6 to 8 weeks It is important to note that the virus of tsutsugamushi is transmitted hereditarily in the mite

Pathology

Unlike many insect borne diseases a local lesion develops at the site of inoculation in tsutsugamushi disease The bite of a non infective mite is followed by a slight but negligible lesion The site of the bite of infective mites is marked by a necrotic area several millimeters in diameter This area is sharply demarcated from the surrounding tissue and eventually becomes covered with a crust Kawamura describes necrosis in the swollen lymph glands and occasionally in the skin rash The spleen often shows moderate swelling and focal necroses have been described in this organ

Inoculation of Animals

Various species of monkeys are susceptible to tsutsugamushi disease The ones which have been used more extensively are *Macacus fuscatus* which is indigenous in Japan *M rhesus* and *Pithecus philippinensis* Monkeys can be infected either by the bite of mites or by th injection of virulent blood After an incubation period of about one week a sharp febrile reaction develops which is accompanied by a leucopenia The reaction lasts for about one week and then the temperature and white count return to normal The animals always recover and they do not show any xanthem

The behavior of guinea pigs is interesting They show no fever nor any reaction whatever yet they harbor the virus This behavior greatly simplifies the task of maintaining a strain of this disease in the laboratory The Japanese investigators have established the practice of subinoculating from guinea pig to guinea pig every 10 or 12 days using blood and spleen for the inoculations After several passages a monkey is inoculated and the characteristic fever and leucopenia develop

milder infection often designated as pseudotyphus has much in common with tsutsugamushi disease but the exact relationship of these two infections has not yet been investigated fully Occasional surveys in China have failed thus far to reveal any instances of tsutsugamushi disease

Etiology

The causative organism has not yet been established thoroughly The evidence points strongly toward the Rickettsia During a visit in the endemic regions of Niigata Professor Kawamura very kindly supplied me with a strain of tsutsugamushi disease the infection being maintained in monkeys and guinea pigs Using a medium made with Martin s peptone, the writer isolated cultures of a Rickettsia like organism from infected guinea pigs Monkeys inoculated with cultures of this organism developed fever and subsequently they did not react typically when given an immunity test with tsutsugamushi virus There has however, been no opportunity to make examinations for this organism either in patients or in mites that are infective

Epidemiology

On the western coast of the island of Honshiu, the mountain streams, which ultimately drain into the Sea of Japan become swollen during the rains of spring and early summer and flood their low lying banks in the valleys As the water subsides a red mite known to the Japanese as akamushi makes its appearance The name "tsutsugamushi' means simply dangerous bug', for the natives of this region recognized long ago that the bite of these mites often was followed by a serious fever During mid summer and early autumn, the danger of visiting these recently flooded areas prevents any but the poorer classes from venturing into them to secure for example mulberry leaves for feeding silkworms Tsutsugamushi disease is only one of several instances in which native people recognized the relationship between arthropods and infectious diseases long before any scientific demonstration was attempted

Observers are not agreed fully as to the exact number of species of the harvest mites which are found in the endemic areas *Trombicula akamushi* is probably the principal and perhaps the sole species that transmits the infection It is closely related to the annoying but harmless 'chigger' mite of our southern states

The virus of tsutsugamushi disease readily propagates itself in nature quite independently of any human cases The life cycle of the mite consists of larval and nymphal stages and each of these phases of development is preceded by a resting period The external features of the adult and nymph are very similar

Complications

A moderate degree of bronchitis is noted frequently as a complication of the more severe cases As in many fevers abortion usually occurs in pregnant women

Immunity

One attack of tsutsugamushi disease affords considerable but not complete protection against reinfection Second attacks may occur within one or two years of the first infection and a few instances of third attacks have been re corded Almost without exception the secondary attacks run a mild course

Diagnosis

In endemic zones the recognition of typical cases is easy in view of the fever the exanthem the history of a mite bite and its local lesion the swollen lymph glands the enlarged spleen and the leucopenia Mild or atypical cases may require extensive laboratory studies in order to identify the nature of the infec tion Tsutsugamushi disease typhus fever and Rocky Mountain spotted fever do not occur in the same geographical area otherwise the interest in diagnosis would be considerably enhanced These three fevers so much alike in man behave very differently in guinea pigs Rocky Mountain spotted fever infects guinea pigs readily and the mortality is high (90 per cent) Typhus fever pro duces only a mild febrile reaction and the animals survive Tsutsugamushi disease does not even produce a febrile reaction in guinea pigs but the virus is conserved In tsutsugamushi disease there is nothing comparable to the Weil Felix reaction as used for the diagnosis of typhus fever For the identification of atypical cases it may be necessary to resort to the inoculation of monkeys followed by extensive studies in the laboratory

Prognosis

As already indicated the mortality in some outbreaks is high (25 to 40 per cent) but in Formosa it is much lower (5 to 10 per cent) A similar variation is seen in the virulence of Rocky Mountain spotted fever and in typhus fever

Treatment and Prophylaxis

There is no specific therapy The usual chemotherapeutic agents are use less and no serum treatment has been developed

Symptomatology

From the clinical symptoms alone it would be difficult to differentiate a case of tsutsugamushi disease from typhus fever except for the local lesion caused by the bite of the mite An infective bite is followed rather promptly, usually in 1 to 3 days by a sharp local reaction The onset of generalized symptoms usually is considered as marking the end of the incubation period This is usually a period of about one week

In typical cases the temperature rises abruptly and is maintained continuously at a fairly high level (e g 103° to 105° F) for about 2 weeks Ordinarily the pulse is proportionate to the temperature and often becomes dicrotic The regional lymph glands draining the site of the bite commonly those of the groin, are tender and swollen sometimes to the size of a pigeon s egg Later there is more or less generalized enlargement of the lymph glands

Late in the first week of fever a maculo papular exanthem develops usually on the trunk and extends promptly to the extremities It often reaches its full development in 3 or 4 days and resembles very much the rash of typhus As the exanthem fades some areas become petechial Occasionally the mucous membranes of the mouth are involved

By the beginning of the second week, the spleen usually is palpable At this time the blood shows a marked leucopenia and the total white count is very often as low as [illegible]000 to 3000 cells per cubic mm The urine often contains albumin and casts

Patients usually complain of headache and pains in the limbs The knee jerk usually diminishes and may disappear In convalescence this reflex some times is exaggerated In severe cases a typhus like state supervenes

In fatal cases death usually occurs during the second week of the disease Patients who are in fair condition in the third week have a good chance of recovery The fever returns to normal gradually in the course of several days The patients are debilitated the return to full health and vigor requires time but there are no ultimate sequellæ

Atypical Cases

The preceding symptoms apply only to characteristic severe forms of tsu tsugamushi disease As would be expected many mild and atypical cases are seen The primary lesion of the infective bite may be negligible in extent or undiscoverable altogether The incubation period may be prolonged, and the ultimate fever and rash may be abortive in character

CHAPTER XVII-B

BLACKWATER FEVER

By COL. CHARLES F. CRAIG, Medical Corps, U. S. Army (Retired), D.S.M.

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INTRODUCTION

Synonyms.—Hemoglobinuric fever, malarial hemoglobinuria, bilious hemoglobinuric fever, remittent malarial hemoglobinuria, hemorrhagic malarial fever. French, fièvre bilieuse hemoglobinurique. German, Schwartzwasserfieber.

Definition.—A disease of disputed origin but undoubtedly closely associated with sub-tertian or estivo-autumnal malarial infection, characterized by the occurrence of attacks of hemoglobinuria caused by the hemolysis of the red blood cells in the general circulation, and accompanied by jaundice and profound anemia.

History

It was not until the latter part of the 19th century that blackwater fever was noted in medical literature. Lebeau first described the disease in Madagascar in 1850, Veretas in Greece in 1858, and the first cases in the United

The only preventive measures at present consist in avoiding the endemic zones. In the Akano river district in Japan the Government is building levees along the river banks to prevent the flooding of the valleys. Workers employed in the construction of these levees are provided with "mite proof" clothing.

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malarial regions has never been observed although the prevailing type of malarial infection is with *Plasmodium falciparum* the sub tertian plasmodium

Europe Blackwater fever does not occur with great frequency in any of the countries of Europe but is most prevalent in Bulgaria Macedonia Greece Sicily and Sardinia It is comparatively rare in Italy even in regions where sub tertian malaria is intense

Americas In the United States blackwater fever is most prevalent in the Southern States especially in certain regions in Florida Georgia Alabama Mississippi Arkansas and Texas It is also present to a lesser degree in North Carolina Virginia and Oklahoma At the present time blackwater fever is seldom observed in the states mentioned

During the building of the Panama Canal blackwater fever was prevalent in Panama and it occurs in the most malarious portions of Central America and in Brazil Venezuela and the Guianas

Despite the immense amount of infection with *Plasmodium falciparum* in our soldiers serving in the most malarial regions in the Pacific blackwater fever was almost absent during the war with Japan probably due to the fact that our troops were all given suppressive treatment with atabrine and that this drug is very efficient in eliminating infections with this plasmodium

Etiology

Theories of Causation

Although there is now a general concensus of opinion that blackwater fever is in some way very closely associated with malaria if not actually caused by it there is still a decided difference of opinion among medical scientists as to the exact causation of this disease and it cannot be stated at this time that the etiology of blackwater fever has been solved The most important of the various theories that have been brought forward as to the etiology of the condition are the following

The Malarial Theory of Origin —The belief that malarial infection is the cause of blackwater fever has been steadily gaining ground and almost all authorities who have studied the disease in the endemic regions accept this explanation of the etiology The belief is based upon the occurrence of blackwater in regions of intense malarial infection with the sub tertian plasmodium *Plasmodium falciparum* and its absence from other regions the finding of the plasmodium and malarial pigment in the blood during the onset of hemoglobinuria in many cases the increase in mononuclear leucocytes the fact that a certain length of residence in an intensely malarial region usually is necessary before the disease develops and the fact that prophylactic measures effective in malaria are equally effective in blackwater fever In certain instances one or more of the factors

States were described by Cummings, in Louisiana, in 1859 It was undoubtedly described by numerous other observers between 1850 and 1860 under the names "remittent malarial hemoglobinuria" and "hemoglobinuric malarial fever" It is remarkable that this condition is not mentioned by Torti, one of the most skilled and accurate students of malaria in Italy, and it was not mentioned by any of the clinicians of India as being present in that country until after the observations of Lebeau and Cummings The comparatively recent appearance of this striking symptom complex in the medical literature of the countries where it is now endemic has led some authorities to believe that the condition is a disease entity recently introduced and that it is impossible to believe that clinicians who were especially interested in the diseases of the tropics and sub tropics would have omitted to describe it had it been present prior to the 19th century Other authorities believe that the condition has always been present in the endemic regions but that the cases were few in number Only when commercial exploitation brought about an influx of susceptible individuals into the endemic areas together with the greatly increased use of quinine by such individuals did the number of cases increase sufficiently to attract attention However this may be, it is a fact that so far as medical history is concerned we have no record of blackwater fever prior to the middle of the 19th century

Geographical Distribution

Blackwater fever is practically absent north of 40° N or south of 0° S It is prevalent in regions where the sub tertian or estivo-autumnal malarial fevers are present but is not always present in such regions It is apparently absent in some intensely malarious localities or occurs very rarely, while in others it may at times assume epidemic proportions

Africa The hot bed of blackwater fever is tropical Africa where it occurs frequently and causes much invalidism among Europeans and many deaths The worst regions are Sierra Leone the Gold Coast Nigeria, the Cameroons the delta of the Niger and Gambia the Congo region and the East Coast in the Zambesi region It also occurs in British East Africa Rhodesia, Uganda Abyssinia the Upper Nile and Madagascar and Reunion

Asia In India blackwater fever occurs only in certain localities where malarial infection is intense and the prevailing type is sub-tertian or estivo-autumnal In the Terrai the Douars Jeypore Amritsar Darjeeling Assam and Siam the condition is frequently encountered and it also occurs in Palestine Tonquin, the Central Provinces of India and Bengal the Malay Peninsula, Burma Yunnan in China Java the Solomon Islands and New Guinea The disease is rarely seen in the Philippines and in some of the most intensely

in the viscera, especially the kidney, spleen and liver but their observations have not been confirmed While the failure to find a specific parasite does not prove that one does not exist it would appear that the evidence is so convincing of the malarial origin of the condition that the specific theory has but little to support it at the present time It is true however that comparatively little experimental work has been attempted as regards specific causation and much remains to be done before one can state positively that blackwater fever is not a disease *sui generis* caused by a specific parasite It is especially desirable that the morphology of the malaria plasmodium associated with the condition be studied more carefully as it is not beyond the range of possibility that a distinct species of malaria plasmodium is the cause of the disease The existence of such a species would explain many of the puzzling features of the epidemiology of the disease

While malaria is the predisposing factor in the production of blackwater fever it is probable that any factor which lowers the resistance may act as an exciting cause Other infections exposure to low temperatures administration of quinine dietic or alcoholic excesses or excessive nervous strain or physical strain may excite an attack as noted by numerous observers

The mechanism of hemolysis in blackwater fever still remains unsolved although many observers have suggested theories in an endeavor to explain the process The hemoglobin is discharged into the blood plasma causing hemoglobinemia and it is estimated that from 60 to 80 per cent of the red blood corpuscles are destroyed within 24 hours There are no definite changes in the morphology of the red blood corpuscles prior to disintegration although Thomson believes that brassy corpuscles are more numerous than in uncomplicated infections with *Plasmodium falciparum* The liberated hemoglobin is excreted by the kidneys and urobilin occurs in increased amounts in the urine In severe infections with *Plasmodium falciparum* there may be some hemoglobinuria which the reticulo-endothelial system takes care of by splitting the hematin into the iron free pigment bilirubin and the iron containing pigment hemosiderin The liberation of hemoglobin in blackwater fever is so great that while the reticulo endothelial system breaks up most of it Neave Kingsbury has shown that from 17 to 36 per cent is excreted in the urine

That hemolytic substances can be extracted from the tissues and urine in blackwater fever has been claimed by Dudgeon and that such substances can also be found in the tissues of fatal sub tertian malarial patients Blacklock concludes that the cause of the hemoglobinuria may be the liberation of sarco lactic acid into the blood stream while Plehn believes that the whole process is an allergic reaction due to repeated sensitization of the body to the proteins of the malaria plasmodium

Some authorities believe that there is a supersensitiveness of the patient to the protein of the malaria plasmodia and more recently Fernan Nunez (1936)

mentioned above are apparently not complied with, but as a whole, the evidence appears to be almost conclusive that malarial infection is essential in the causation of blackwater fever The observations of Deeks and James, Arkwright and especially those of J G Thomson, who showed conclusively that blackwater fever occurs only in regions where infections with *Plasmodium falciparum*, the sub tertian plasmodium are numerous, practically demonstrate that blackwater fever is a symptom complex sometimes occurring in this type of malaria although apparently well authenticated instances of its occurrence with tertian and quartan malaria have been recorded

Foy (1938) has reported the occurrence of blackwater fever in patients suffering from infections with *Plasmodium vivax*, no less than 33 per cent of the cases observed by him being infections with this plasmodium, and Fairley (1939) has observed the occurrence of this condition in a patient infected with *Plasmodium ovale* which resulted fatally Ciuca has reported the occurrence of blackwater fever in a patient who had been inoculated with *Plasmodium knowlesi*, of the monkey for therapeutic purposes

It is thus evident that this condition may occur in infections with all of the human malaria plasmodia but that they are very rare as compared with the large number of patients who develop the condition after infection with *Plasmodium falciparum*

The Quinine Theory of Origin — The observation that the administration of quinine frequently precipitates an attack of blackwater fever led Koch to consider that quinine is the cause of the disease It is undoubtedly true that quinine even in small or moderate doses may if an attack of blackwater fever is impending precipitate the attack but the theory that this drug is responsible *per se* for the disease has been practically abandoned In susceptible individuals quinine produces hemoglobinuria but this type of hemoglobinuria is not true blackwater fever and develops within an hour after the administration of the drug True blackwater fever has been observed often in individuals who have not taken quinine for long periods of time before the appearance of symptoms

The Specific Theory of Origin — The clinical resemblance of blackwater fever to hemoglobinuria caused in animals by the piroplasms the peculiar distribution of the disease the fact that cases have been observed when infection with malaria apparently could be excluded and the rarity of the condition in many regions where estivo-autumnal malaria is intense has led many authorities to the conclusion that the disease is caused by a specific parasite The most careful search has been made for a piroplasma but neither the examination of the blood material obtained by splenic puncture nor sections of the viscera have resulted in the demonstration of such an organism in blackwater fever Schuffner and Snijders in Sumatra found a leptospira resembling *Leptospira icterohemorrhagiæ* in a case presenting the symptoms of blackwater fever The organism occurred

incidence of the condition as late summer and autumn in the United States August and September in West Africa and May and August in Central Africa This seasonal incidence corresponds with the seasonal intensity of estivo-autumnal malaria in the regions mentioned

While in the endemic regions the number of cases of blackwater fever is very small in comparison with the number of malarial infections the occurrence of the condition in epidemics has been reported by Sambon Wenyon Plehn and others in which numerous cases occurred within a short period of time The occurrence of such epidemics is difficult to explain upon the basis of the malarial theory of causation It has also been noted that the condition occurs in individuals in the endemic regions who never suffered from malaria and Manson states that officers of the African colonial service were frequently attacked by blackwater fever while in perfect health There are numerous instances of record where the inhabitants of certain houses have developed blackwater fever while those of surrounding habitations situated identically so far as opportunities for acquiring malaria are concerned have escaped Here again the malarial theory of causation fails to explain the facts

It is evident that our knowledge of the exact etiology of blackwater fever is still in an unsatisfactory condition and while the malarial nature of the condition is best supported by evidence that evidence is still incomplete and many of the phenomena noted in the epidemiology of the disease remain unexplained There is no doubt that blackwater fever is closely associated with malaria especially with sub-tertian or estivo-autumnal infections but it cannot be truthfully stated that its malarial origin is indisputably proven even today

PATHOLOGY

The principal pathological changes occur in the kidneys spleen liver blood and the urine

The Kidneys —The kidneys are always congested and present the usual changes noted in acute venous congestion or acute nephritis The capsule is not adherent the cortex is thickened the intertubular capillaries congested and the general appearance of the section that of an acute tubular nephritis Microscopical examination shows marked epithelial desquamation in the tubules congested capillaries and congested and necrotic Malpighian tufts In those instances in which death occurs after three or four weeks from the onset of hemoglobinuria the kidneys present the lesions of a sub-acute parenchymatous nephritis In practically every instance the epithelial cells of the tubules contain considerable yellowish pigment derived from the broken-down red corpuscles and in cases where there have been repeated attacks of malaria pigment is present in varying amounts In many cases no malaria pigment can be demon

has brought forward evidence that the attack of blackwater fever is an acute allergic reaction to this protein MacGilchrist has shown that an acidosis is present in blackwater fever in patients who have a diseased liver, and that this plus malaria and the administration of acid salts of quinine brings about the attack, while Fairley and Bromfield (1934) have found that the hemolytic agent in this condition arises from a metaplastic breakdown in malignant malaria which may be caused by the administration of quinine or plasmochin

From the many theories of the causation of blackwater fever that have been published it is evident that none of them really demonstrates the cause of the hemolysis although some of them are supported by very suggestive evidence

Epidemiology

There are several mysterious problems connected with the epidemiology of blackwater fever that have never been solved Its occurrence in some districts intensely infected with *Plasmodium falciparum* and its almost complete absence from others with as heavy an infection rate with this plasmodium its frequent occurrence in specific houses the so called blackwater fever houses its occurrence in epidemic form its disappearance for long periods of time in endemic regions and its unexplained reappearance are all problems that as yet have not been satisfactorily explained if the real cause of the disease is infection with *Plasmodium falciparum*

All ages and both sexes are susceptible but it is most commonly observed in adult males and in Europeans living in regions where malaria is common and pernicious in type There is no racial immunity although the natives in endemic regions who have developed an immunity to malaria through repeated attacks in early life do not suffer from blackwater fever Conditions that decrease resistance as starvation a poorly balanced diet exhausting diseases chilling and hardships of any kind predispose to the condition The usual period elapsing between settling in an intensely malarial locality and the development of blackwater fever is between one and two years but numerous instances are on record in which an attack occurred within six months and several in which the condition developed within a few weeks after entering the endemic area While there is usually a history of repeated malarial paroxysms before the onset of hemoglobinuria the condition may occur in individuals who have never developed symptoms of malarial infection prior to the attack of blackwater fever The condition is often observed in individuals in regions where malaria is absent but only when such individuals have resided previously in malarial localities Such individuals often give a negative history of malaria and these cases are explained by the probable existence of a latent malarial infection the first symptoms of which are those of blackwater fever In endemic regions there appears to be a seasonal

Albumin is present in large amounts and albuminuria may persist during convalescence

SYMPTOMATOLOGY

Period of Incubation — The period of incubation is unknown It would appear that blackwater fever may rarely appear after only a few days residence in the endemic centers although in the vast majority of cases a much longer residence is required Manson mentioned cases in which the condition appeared for the first time in Europeans who had been absent from the infected localities for months and as already mentioned it is most frequently observed in individuals who have resided for at least a year in a malarial region

Manson Bahr and others recognize a pre blackwater state in which the patient who has suffered from several attacks of malaria due to *Plasmodium falciparum* presents a sallow skin jaundiced conjunctivae enlarged congested and tender liver enlarged spleen and suffers from persistent headaches The urine is dark in color contains a small amount of albumin and an increased amount of urobilin while the blood shows a small number of ring forms of *Plasmodium falciparum*

Symptoms — In practically all cases the attack begins suddenly with a chill after which the temperature rises rapidly to 103° F (39 4 C) or higher The chill usually is severe but may be so slight as to be hardly noticeable The usual symptoms of fever are present as malaise pain in the muscles and articulations loss of appetite and mental depression The pain often is very severe over the loins liver and spleen while pain in the bladder is often noted After the symptoms are well pronounced there is a marked desire to urinate and the urine passed is of the characteristic dark brown or port wine color which gives the name blackwater to the condition The fever may be intermittent or almost continuous in type and in many instances jaundice slowly develops and may become a marked symptom of the attack Tympanites is a common symptom and pain in the epigastric region is elicited upon pressure Bilious vomiting usually is present most marked in severe cases and has given the name bilious remittent fever to the condition The termination of the attack in patients who recover usually is by crisis the temperature receding accompanied by profuse perspiration while the hemoglobinuria disappears Great prostration often is observed after an attack of blackwater fever and convalescence may be much delayed by recurrences of hemoglobinuria and fever or of fever alone The hemoglobinuria may be so mild as to last for an hour or two only or it may persist at intervals for weeks As the hemoglobinuria disappears the urine which may have been greatly decreased in quantity at the height of the attack increases in quantity becomes lighter in color and is passed

striated Many of the straight and collecting tubules contain plugs of granular material eosinophilic in reaction when stained, and hemoglobin, granular and hyaline casts are present

The Spleen — The spleen is enlarged, decreased in consistency and somewhat yellowish in color If there have been repeated attacks of malaria, the spleen may be much pigmented and increased in consistence The capillaries are congested and may contain large endothelial cells enclosing malaria pigment and degenerated plasmodia but frequently it is difficult, or impossible, to demonstrate the presence of malaria pigment in the spleen A characteristic lesion is a widespread necrosis of the Malpighian bodies, which according to Whipple, may involve practically every Malpighian body in the spleen A large amount of yellow pigment usually is present in the spleen

The Liver — The liver is enlarged, decreased in consistence and usually yellowish in color Sections show cloudy swelling of the liver cells which are filled with yellow pigment the capillaries are congested and areas of focal necrosis are frequently observed Malaria pigment may or may not be present, and the capillaries may contain macrophages loaded with pigment and degenerated plasmodia or these may be entirely absent

The Blood — The blood is yellowish red in color and less viscid than normal There is a great reduction in the number of red blood corpuscles due to hemolysis but the undestroyed corpuscles appear normal in size and shape during the early stage of the disease although paler in color At the beginning of the attack malaria plasmodia may be found in the erythrocytes but soon disappear and free pigment or pigmented leucocytes may also be found in many cases The reduction in hemoglobin parallels that of the reduction in erythrocytes and the alkalinity and coagulation time of the blood are reduced also Following the paroxysm there is a marked leucopenia with an increase in the large mononuclear and transitional leucocytes At this time there is a profound polychromasia induced by the rapid development of new red cells At the beginning of the attack hemoglobinemia may or may not be present

The Urine — The color of the urine is usually a dark cherry red but it may be almost black or in mild cases a brownish yellow Spectroscopic examination shows the characteristic bands for oxyhemoglobin and methemoglobin the former in severe cases and the latter in the milder cases The reaction is alkaline the specific gravity generally low and if the urine is placed in a sedimentation glass it separates into two distinct layers the upper clear and brown or dark red in color and the lower brownish grey in color consisting of a sediment composed of yellowish granular debris numerous hyaline and hemoglobin casts degenerated epithelium and a very few red blood corpuscles Crystals of hematoidin may be present but bile pigments usually are absent A large amount of urobilin is present and this increased amount may persist for some time during convalescence

pleurisy pneumonia neuralgias and chronic enteritis have all been reported as sequelae of blackwater fever

DIAGNOSIS

Of the diseases which may be confused with blackwater fever may be mentioned yellow fever paroxysmal hemoglobinuria pernicious malaria of the bilious remittent type Weil s disease and quinine hemoglobinuria

In *yellow fever* jaundice does not begin until the third or fourth day hemoglobinuria is absent albuminuria occurs from the second to the fourth day and the temp rature curve is characteristic Hematuria may occur in yellow fever the pulse is slow in relation to the temperature and vomiting does not usually occur at the onset *Paroxysmal hemoglobinuria* in a region where blackwater fever is endemic is most difficult to differentiate but in most cases the greater severity of the symptoms in blackwater fever will serve to make a diagnosis possible *Pernicious malaria* of the *bilious remittent type* is said to cause confusion but the presence of the malaria plasmodia in the peripheral blood until quinine is administered the prompt subsidence of the symptoms under quinine treatment and the absence of hemoglobinuria should enable one to diagnose the malarial nature of the condition without difficulty *Weil s disease* is characterized by a jaundice developing in from 48 to 72 hours by a polynuclear leucocytosis and the absence of hemoglobinuria although there may be h maturia *Quinine hemoglobinuria* is easily differentiated from blackwater fever by the ab ence of the acute symptoms characteristic of that condition i s occurrence in localities known to be free from blackwater fever and the prompt disappearance of the hemoglobinuria upon cessation of the administration of quinine

The *laboratory diagnosis* of blackwater fever rests upon the demonstration of the existence of hemoglobinuria Spectroscopic examination of the urine will show the spectrum of oxyhemo lobin and of methemoglobin while the rapid reduction in the erythrocyte count demonstrates tl e rapidity of red cell destruction The urine also shows an increase in urobilin the absence of red blood cells except rarely in very small numbers and the presence of much albumin and of hemoglobin granular and hyaline casts The presence in the blood of large endothelial cells containing decolorized red blood corpuscles is characteristic of blackwater fever In the differentiation of paroxysmal hemoglobinuria the determination of the autolytic activity of the blood is useful If 5 c c of the patient s blood is placed in a small test tube the tube placed on ice for five minutes and then incubated at 37 C for one hour no change results in the case of blackwater fever but in paroxysmal hemoglobinuria very marked hemolysis occurs

The occurrence of the following symptoms is practically diagnostic of blackwater fever marked chill with succeeding irregular temperature epigastric

with less discomfort to the patient The acute attack may last for a day or two only or may be prolonged over several days Diarrhea is a common symptom but constipation may be present

In fatal cases the temperature rises to 104° F (40 ° C) or higher, there is severe and prolonged bilious vomiting, bilious diarrhea great pain in the epigastric region and the loins and a gradually developing somnolence which deepens into a fatal coma In some instances the symptoms in the fatal cases are those of uremia due to a total suppression of the urine or to the development of nephritis while in others the fatal symptoms are those of severe hemorrhage or death may occur from hyperpyrexia or the typhoid state may develop A marked decrease in the amount of urine passed in twenty four hours is always an unfavorable symptom

The following clinical data are of much importance in the symptomatology of blackwater fever the temperature curve is not at all characteristic of the condition hemoglobinuria is always present but unless accompanied by other symptoms, as fever vomiting and jaundice cannot be considered as peculiar to this disease, the bilious vomiting is so constant as to be an important confirmatory symptom, but alone is of no value, the microscopic character of the sediment of the urine is not characteristic as the same elements are found in hemoglobinuria due to other causes the development and persistence of jaundice is very characteristic when accompanied by the other symptoms noted

The *physical signs* during an attack of blackwater fever consist in marked tenderness and pain upon pressure over the epigastric region an enlarged and tender liver and spleen and a jaundiced condition of the conjunctivae and skin A systolic murmur at the apex of the heart hemic in character and not transmitted is often present There may be an acute bronchitis developing shortly after the onset of the attack and there is generally some evidence of congestion and edema of the lungs Anemia as disclosed by the red blood count may be marked the red cells numbering less than 3 000 000 per cu mm but if counts are made after the symptoms have disappeared the reduction in the erythrocytes is seldom as great as one might expect owing to the rapid replacement of the destroyed cells The pulse at first is rapid and of high tension but later becomes weak easily compressible and thready An increase in rate to over 130 is an unfavorable symptom, and in fatal cases the pulse rate may be over 150 beats per minute

Complications and Sequelae

These are few in number diarrhea and dysentery being the most frequent of the complications while nephritis is the most common sequela Anemia is a frequent sequela but under proper treatment is rapidly eliminated Parotitis,

Treatment

The patient suffering from hemoglobinuric fever even though of mild character should be confined to bed the body warmly covered and warm alkaline drinks should be administered to maintain the body heat The bowels should be opened by the administration of calomel in small doses or by magnesium sulphate and if there is evidence of suppression of the urine diuretics as potassium citrate should be freely administered hot fomentation applied over the kidneys and an exclusive milk diet enforced If vomiting be slight liquid nourishment may be given at short intervals but in cases in which the vomiting is severe nutrient enemata should be given The rectal injection of 250 c c (half a pint) of normal saline to each 500 c c. (pint) of which 8 gm (1 0 grains) of bicarbonate of soda have been added should be repeated every hour or the drip method may be used In cases in which anuria or collapse occurs the prompt intravenous injection of normal saline may save life and the subcutaneous injection of from 250 to 500 c c of normal saline once or twice daily is recommended by several authorities

The vomiting may be benefited by the application of mustard plasters over the epigastrium the sucking of cracked ice the drinking of carbonated beverages and the sipping of champagne As a last resort morphine may be administered but this drug should never be used if it can be avoided The administration of 0 6 c c (10 minims) of 1 to 1 000 adrenalin solution in water often is efficacious in relieving hiccough and vomiting

The fever seldom requires treatment as the temperature is not excessive and seldom continues for many days but in cases in which hyperpyrexia occurs sponging with tepid water and alcohol usually is sufficient Antipyretics should not be used in the treatment of this condition

Assuming that blackwater fever is of malarial origin the question of the advisability of giving quinine in this condition is a most important one If malaria plasmodia are found in the blood at the beginning of the paroxysm some authorities believe that this drug should be administered but when one remembers that these plasmodia will rapidly disappear owing to profound hemoglobinuria it is more than doubtful if the drug should be given even though plasmodia may be present The added fact that quinine is capable of producing hemoglobinuria in certain individuals again speaks against the use of this drug in blackwater fever However if the plasmodia continue present after two days quinine may be administered commencing with very small doses [illegible] mgm ($\frac{1}{30}$ grain) and gradually increasing until from 0 1 to 0 13 gm (1 5 to 2 grains) are being given every two hours The drug should not be given during convalescence unless malaria plasmodia are found in the blood and in such cases fractional doses of the drug should be given every two or three hours until the patient is

pain or distress with nausea and vomiting of bile stained material, passage of dark brown or red urine in which red blood cells are absent or present only in very small number, an enlarged and tender liver and an enlarged spleen, severe anemia marked albuminuria with hemoglobin and granular casts in the urine, early jaundice and severe prostration

Prognosis

The prognosis always should be guarded and generally is grave The mortality varies from 10 to 30 per cent Some attacks are so mild as hardly to be recognized but in the majority of cases the prognosis is uncertain and depends upon the character and severity of the symptoms present Unfavorable prognostic signs are anuria excessive bilious vomiting continued hiccough and somnolence Sudden death has been reported from thrombus formation in the large vessels or the heart Convalescence is complicated by the presence of severe anemia in many cases and may be prolonged from other causes

The mortality of blackwater fever appears to vary in different localities and following treatment with quinine Deaderick states that cases treated with quinine had a mortality of 25 9 per cent, while those untreated had a mortality of only 11 1 per cent Manson Bahr states that patients having a recurrence of blackwater fever in London had a mortality as high as 50 per cent In Japan the mortality has been 33 per cent in Calcutta 20 per cent and in Rhodesia it has averaged about 1 per cent in nearly 2 000 cases observed in that country

One attack of blackwater fever does not protect against others but apparently predisposes to other attacks In about 20 per cent of cases a second attack has been observed in Nigeria and a third attack is said to be almost invariably fatal

The regeneration of the blood usually is rapid after the attack the erythrocytes showing marked stippling and polychromasia while normoblasts and reticulocytes often occur in very large numbers in the peripheral blood

Prophylaxis

Measures that have been recommended in the prophylaxis of malaria are efficient also in the prophylaxis of blackwater fever for if malaria is prevented blackwater fever will not occur in any locality Enough has been stated in discussing the etiology of this condition in the present contribution to indicate what general measures should be taken in prophylaxis and it should be remembered that people long resident in malarial regions appear to be much more susceptible to an attack of blackwater than new comers because older residents have been more exposed to malaria infection and usually have suffered from repeated attacks The avoidance of chilling and other conditions which lower resistance is especially important in the prophylaxis of this condition

TREATMENT

The patient suffering from hemoglobinuric fever even though of mild character should be confined to bed the body warmly covered and warm alkaline drinks should be administered to maintain the body heat The bowels should be opened by the administration of calomel in small doses or by magnesium sulphate and if there is evidence of suppression of the urine diuretics as potassium citrate should be freely administered hot fomentation applied over the kidneys and an exclusive milk diet enforced If vomiting be slight liquid nourishment may be given at short intervals but in cases in which the vomiting is severe nutrient enemata should be given The rectal injection of 250 c c (half a pint) of normal saline to each 500 c c (pint) of which 8 gm (120 grains) of bicarbonate of soda have been added should be repeated every hour or the drip method may be used In cases in which anuria or collapse occurs the prompt intravenous injection of normal saline may save life and the subcutaneous injection of from 250 to 500 c c of normal saline once or twice daily is recommended by several authorities

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taking 0 13 gm (2 grains) every two hours and this dosage continued for a month, or 0 2 gm (3 grains) may be taken every three hours for five doses Before each dose 0 6 gm (10 grains) of sodium bicarbonate is given in water The method of administration of quinine given above is that recommended by Megaw who has found it satisfactory in his practice but he states that even with as small a dose of quinine as 30 mgm (½ grain) hemoglobinuria returned in one case The drug should be discontinued at once, if the hemoglobinuria returns

The employment of plasmochin and atabrine in the treatment of blackwater fever has been recommended by several observers, but at the present time it appears to be the consensus of opinion that neither of these synthetics should be so employed until convalescence has been established Plasmochin theoretically should be able to activate an attack of blackwater fever, as it is well known to be capable of producing methemoglobinuria but despite this several eminent clinicians have recommended its use in the treatment of blackwater fever while others have recommended atabrine in treatment, but despite the favorable reports which have been published regarding these drugs it cannot be said that at present they establish their harmlessness, when so employed and it is the part of wisdom to abstain from using them until convalescence has been well established when they may be employed to eliminate a malaria infection if it still be present

The following method of treatment has been recommended by the Office of the Surgeon General of the United States Army and embodies the best present day methods of treatment

Circular Letter No 56 War Dept Office of the Surgeon General Washington 1942 recommend the following *treatment*

(1) *Do NOT give quinine or atabrine* until convalescence from the attack of blackwater fever is established

( ) Absolute rest in bed Keep patient warm

(3) Give a minimum of 2 000 c c of fluids per day much more if possible

(4) During the period of vomiting if urine is acid or anuria exists give 1 000 c c of normal saline or of 5 per cent glucose This can be repeated after 12 hours if urine remains acid

(5) When vomiting is controlled give sodium bicarbonate 0 6 grams (10 grains) by mouth every 1 to 2 hours until urine is alkaline to litmus thereafter give only if urine becomes acid

(6) If unable to void catheterize every 4 hours in order to determine urine output and reaction to litmus

(7) For severe anemia give transfusions repeated daily as needed

(8) After convalescence is established if plasmodia are present in the blood give atabrine 0 1 gram 3 times daily for 5 days Watch for recurrence of hemoglobinuria as atabrine has occasionally precipitated an attack

Prevention —(1) Treat every case of estivo autumnal malaria to complete cure

(2) Recurrence of blackwater fever is common especially in the tropics Send patient to temperate zone if possible

Stimulants are indicated in most cases but alcohol should be avoided with the exception of champagne administered as recommended above Strychnine digitalis strophanthus and aromatic spirits of ammonia are all useful when properly administered

During convalescence the diet should be liquid at first followed by an ample nutritious one as soon as the gastric irritability has disappeared Tonics as iron arsenic and strychnine should be administered during convalescence and for some time afterwards and if the anemia is pronounced the administration of liver extract is indicated The patient should be warned against over-exertion and the use of alcoholics and every measure should be taken to avoid mental worry and nervous excitement If possible the patient should leave the endemic locality and never return to it for a longer residence will often result in recurrences of the hemoglobinuria It should be remembered that there is no immunity established by an attack of blackwater fever but that on the contrary susceptibility is increased and recurrences of hemoglobinuria are observed even though the patient may have left the endemic region while such recurrences are very apt to occur, if the patient continues to reside where he experienced his first attack Owing to the undoubted close relationship of estivo-autumnal or sub tertian malaria to blackwater fever the patient should not live in any region where this type of malarial infection is endemic

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February 1 1947

CHAPTER XVIII

DENGUE

By COL CHARLES F CRAIG Medical Corps, U S Army D S M

Table of Contents

Introduction

Synonyms —The synonyms of dengue fever are very numerous but the following are the most important break bone fever (American) ankle fever (Dutch Colonies) break heart fever (American) pere des genoux (Egyptian) fievre rouge (Syrian) three-day fever (India) seven-day fever (India) giraffe fever bouquet fever and many other purely local names derived from the most prominent symptoms which may have been present during certain epidemics

Definition —Dengue is an acute specific fever of short duration caused by a filtrable virus transmitted from man to man by mosquitoes of the genus *Aedes* (*Stegomyia*) It is characterized by a fever usually lasting from five to seven days with sudden onset severe pain in the muscles bones and joints headache postorbital pain backache and prostration In typical cases the temperature drops on the third or fourth day and rises again in from twenty four to forty-eight hours with a recurrence of the principal symptoms There is

a marked leucopenia with an increase in the relative number of the lymphocytes, and skin eruptions which vary considerably in appearance in different individuals. The disease is endemic and epidemic in most sub-tropical and tropical localities and frequently occurs as an epidemic in temperate regions when conditions are favorable.

History

Boylon in Java in 1779 was the first to describe partially dengue followed by Rush in 1780 who called it "bilious remittent fever". In 1903 Graham proved that mosquitoes transmitted this infection and Bancroft in 1906 and Cleland, Bradley and McDonald in 1916 proved that *Aedes aegypti* was the mosquito usually concerned in its transmission. In 1907 Ashburn and Craig proved that dengue is caused by a filtrable virus, and in 1945 Sabin and Schlesinger passed the virus through mice and found that it became attenuated and could be employed in preventive vaccination.

Geographical Distribution

Dengue is endemic in many tropical and sub-tropical countries and frequently becomes epidemic in such regions. In the temperate zones dengue is also epidemic at times, and the literature contains accounts of many widespread epidemics in various parts of the United States. Thus epidemics have occurred as far north as Philadelphia and numerous epidemics have occurred in the states of Georgia, Alabama, Mississippi, Louisiana, Texas and Florida, and less frequently in the states bordering upon the Atlantic south of Pennsylvania. Dengue is especially prevalent in the Philippine Islands and in certain parts of Australia and it is from the study of the disease as it occurs in these countries that most of our knowledge of its etiology and method of transmission has been derived. The infection also is very prevalent in the tropical portion of the Orient and it was in Syria that the first successful experiments regarding its transmission by mosquitoes were conducted. Epidemics have occurred in all of the countries bordering upon the Mediterranean, in Mexico, Central America, and almost all of the countries of South America, as well as in the West Indies and the principal islands of the South Seas. Extensive epidemics have occurred in India, China, Persia, Java, Formosa and Sumatra and in practically all of the ports of the Red Sea.

Etiology

Until the researches of the writer and Ashburn in the Philippines in 1906–1907 dengue was believed to be due to a bacterium and to be one of the most contagious of all infections. No bacterium had been demonstrated as its cause, although

several had been suspected and in 1903 Graham claimed to have found a protozoan organism in the blood which he regarded as the cause of the disease His observations were not confirmed nor has any other organism been demonstrated to cause dengue Ashburn and Craig in 1907 demonstrated that dengue is caused by a filtrable virus which is present in the peripheral blood during the first four days of the disease that it could be transmitted mechanically by *Culex quinquefasciatus* that certain individuals are immune to dengue and that the disease is not contagious All of these observations have been confirmed by numerous other workers and much has been added to our knowledge of the virus since the work of Ashburn and Craig whose researches were made possible by soldiers of the United States Army who volunteered for the experiments It has been proven that the virus of dengue is very minute and that it may be frozen and remain virulent for some time Simmons St John and Reynolds 1931 found that it could not pass through the unbroken skin and that it is filtrable as it occurs in the transmitting mosquitoes Siler Hall and Hitchens 1926 demonstrated that the virus is present in the blood of the patient for several hours before the occurrence of clinical symptoms and remains in the blood in an infective condition for three days after symptoms occur and more rarely for 3 days as shown by Ashburn and Craig (1907)

Until the recent work of Sabin and Schlesinger it was believed that all of the lower animals with the exception of monkeys were immune to dengue but these observers in 1945 were successful in propagating the virus in mice for several generations They have passed it through 16 serial passages in mice and have produced dengue in man with this virus finding that it becomes markedly attenuated during passage and then can be employed in protective vaccination

Prior to the work of Sabin and Schlesinger Simmons St John and Reynolds in the Philippines produced infection in monkeys *Macacus philippinensis* and also in monkeys caught in Java and they believe that these animals may act as reservoirs of the disease as in yellow fever The guinea pig has been infected by Blanc Caminopetros and Manoussakis 19 8 and the blood of such guinea pigs became infective to man in 5 days after inoculation

Epidemiology

Insect Transmission — It has now been demonstrated beyond question that dengue fever is transmitted to man by certain species of mosquitoes and in no other way under natural conditions It is not contagious and patients suffering from it do not need to be isolated if they be placed in mosquito proof wards or rooms Graham in 1903 was the first to produce dengue by the bites of infected mosquitoes and believed that the mosquito concerned was *Culex quinquefasciatus* but it has since been proven that *Aedes aegypti* is the most common transmitter

although other mosquitoes as *Aedes albopictus, Aedes scutellaris hebrideus Armigeres obturbans* and others may transmit the disease when present in the infected regions

After biting a dengue patient, the transmitting mosquitoes become infective to man in from 10 to 12 days but in some instances the mosquito may become infective in 8 days as shown by Schule (1928), or not until 20 to 23 days after biting The period in the mosquito appears to vary with the temperature and probably with the amount of virus ingested by the insect After becoming infected the mosquito remains so for life as demonstrated by Siler, Hall and Hitchens, 1926 who also proved that the infection is not hereditary in the mosquito Simmons, St John and Reynolds found that the dengue virus could be transmitted

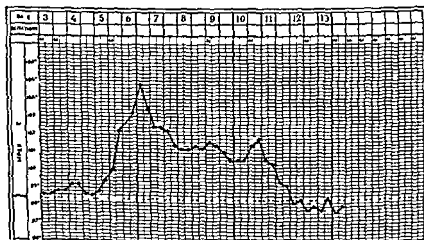


Fig 1 — Temperature Curve of Dengue Fever produced by Intravenous Injection of Unfiltered Blood from Dengue Patient (Ashburn and Craig)

from mosquito to mosquito by copulation and by regurgitation of blood from the stomach which sometimes occurs if they are interrupted in feeding If such flies immediately fed upon another individual blood often is regurgitated from the stomach and infection of the second individual might result if the individual originally bitten was suffering from dengue

Mosquitoes may become infected with the dengue virus if they bite an infected individual during the last day of the incubation period or for from 3 to 4 days after the appearance of symptoms after which time the virus is not present in sufficient amount to infect the mosquito

Mechanical transmission of dengue by other species of mosquitoes than those mentioned is possible although it probably rarely if ever, occurs in nature Ashburn and Craig (1907) produced infection in man by allowing a large number

of *Culex quinquefasciatus* to bite volunteers shortly after the mosquitoes had bitten an infected individual and Simmons St John and Reynolds 1931 confirmed this experiment so that it is possible that if several mosquitoes and probably, other arthropods bite man under such conditions, dengue may be thus transmitted

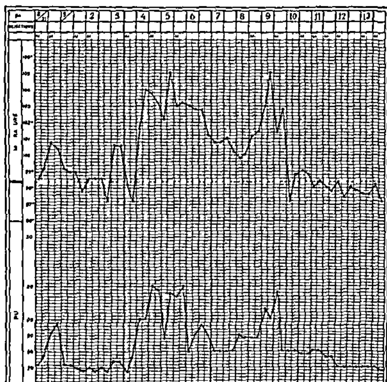


Fig 2 — Temperature Curve of Dengue Fever produced by Intravenous Injection of Filtered Blood from Dengue Patient (Ashburn and Craig)

Dengue spreads very rapidly when introduced into a locality and within a few weeks almost the entire population will have become infected Natural immunity exists but is relatively rare Ashburn and Craig 1907 were unable to infect some individuals either by direct inoculation of the blood of dengue patients or by intravenous injection of filtered blood, but one attack does confer a limited immunity lasting for something over one year as a rule Convalescent serum does not protect against the disease An interesting and important observation made by Simmons in 1931 was that monkeys examined in endemic regions of

dengue were immune to dengue while those brought into such regions from uninfected regions could be infected

There is a great similarity between dengue and yellow fever as described by Craig in 1911 but an attack of dengue does not protect against yellow fever as proven by Dinger and Snijders (1931)

While dengue is one of the most rapidly spreading of all infections it is never contagious as proven by Ashburn and Craig (1907) and all subsequent workers It depends entirely upon transmission by infected mosquitoes and its prevalence upon the number of such mosquitoes and the presence of infected individuals It is usually a disease of subtropical or tropical countries, and frost quickly terminates an epidemic as it destroys the transmitting mosquitoes

Pathology

Comparatively little is known regarding the pathology of dengue as it is almost always a non fatal disease unless accompanied by some fatal complication Heiser (1937) reported a fatal case in which no pathology was observed beyond enlargement of the internal lymph nodes while Photakis observed myocardial degeneration and enlargement of the liver in fatal cases Manson Bahr (1940) states that pulmonary and intracranial inflammation were observed most frequently in fatal cases and Strong (1942) states that encephalitis and nephritis have been observed The only epidemic of dengue in which a mortality of any consequence was observed was that which occurred in Greece in 1928 in which the death rate was approximately one per cent but it is more than probable that many of the fatal cases were due to some other cause

General Pathology

The general pathology of dengue is practically unknown owing to the non fatal character of the infection Scattered reports appear in the literature describing localized cerebral and pulmonary inflammatory lesions thought to be due to the infection and serous effusions into the joints and inflammatory conditions of the crucial ligament of the knee joint have been noted by some authorities When death has occurred from some intercurrent disease the pathology present has not differed from that characteristic of the disease causing death

Special Pathology

While little is known of the general pathology of dengue numerous investigators have contributed much to our knowledge regarding the changes in the blood which occur during the progress of the infection A very careful study of the blood was made by Ashburn and the writer during our investigation of this disease and we found that no anemia occurs during the infection in un

complicated cases the red blood cell count remaining normal as well as the hem oglobin and color index Our observations confirmed the previous ones of Car penter and Sutton and other investigators so that if the cause of dengue lives upon or within the red blood corpuscles it evidently does not destroy them The morphology of these cells is unchanged the staining reactions are normal and no abnormal cells occur

Although no change occurs in the red blood cell count in dengue our studies and those of Vedder [9] demonstrated that a marked leucopenia with an increase in the relative number of lymphocytes usually was present in this disease These observations confirmed those of Carpenter and Sutton and of Stitt and have been confirmed since by Siler Hall and Hitchens In the vast majority of cases there is a well marked leucopenia present throughout the attack and this fact is of considerable diagnostic importance The leucocyte count varies all the way from 1 00 leucocytes per cu mm the lowest to 5 000 leucocytes per cu mm the highest the average counts being between 3 500 and 3 800 leucocytes per cu mm The leucopenia is progressive in character being most marked upon the fifth and sixth days of the disease but exceptions to this rule have been noted In some cases a leucopenia is not present and in Siler Hall and Hitchens cases they noted that 25 per cent failed to show a leucopenia at any stage of the disease a much higher percentage than has been noted by other investigators

The differential leucocyte count in dengue is also significant for there is not only a marked reduction in the number of the leucocytes in most cases but a relative increase in the lymphocytes This subject has been investigated by Carpenter and Sutton Stitt Vedder Ashburn and Craig and others and it is well established that in this disease the polymorphonuclear neutrophilic leucocytes are greatly decreased in number and the lymphocytes increased during an attack of dengue fever Vedder has shown that there is an increase in the small lymphocytes early in the disease while the large mononuclears are moder ately increased during the latter days of the infection Stitt found that the small lymphocytes were increased greatly in number early in the disease succeeded by an increase in the large lymphocytes and this by a very marked increase in the large mononuclears In the counts made by Ashburn and the writer we found that the small lymphocytes outnumbered the large during every stage of the infection Siler Hall and Hitchens conclude that the differential counts are of little diagnostic importance as compared with the total leucocyte count but Vedder rightly regards the differential count as of great value in the differen tial diagnosis between dengue and yellow fever the differential leucocyte count in the latter disease being practically normal in the vast majority of cases The *writer regards the leucopenia with the increase in lymphocytes as of much diagnostic value* but it should be remembered that other infections occur in which a similar blood picture may be present

Many observers have described an increase in the eosinophiles as characteristic of dengue and while in many cases there is a definite increase in the number of these cells it cannot be regarded as of any marked diagnostic significance, and it does not occur at all in many individuals

Simmons St John and Reynolds (1931) in their studies upon dengue produced experimentally in human volunteers, found that a marked increase occurred in the immature polymorphonuclear cells of the blood and they regarded this "shift to the left" in the Schilling count of great diagnostic value Taken together with the marked leucopenia, which occurs in this disease, the shift to the left in the Schilling count is almost pathognomonic of dengue fever Simmons and his co workers found that it persisted through the attack and that the leucopenia began upon the second day of the disease and progressively increased to the fourth or fifth days at which time the leucocytes averaged about 2,000 per cu mm of blood

Symptomatology

In considering the symptomatology of dengue it should be remembered that the clinical picture differs markedly in different epidemics and in different individuals Typical dengue exists and it is probable that the majority of cases present the clinical picture which has been recognized as characteristic of the disease but there are many clinical variations and the symptoms present may be so slight as to be almost unrecognizable or so severe as to resemble those of certain fatal infections as yellow fever

Period of Incubation — In the majority of descriptions of dengue fever the period of incubation is given as from three to five days, but authorities have described a period of incubation as short as twenty four hours and as long as ten days In the experimental work of Ashburn and the writer by direct inoculation of the blood of dengue patients into healthy individuals the period of incubation varied from two and a half to seven days, the average period being three days and fourteen hours The period of incubation after the bites of infected mosquitoes usually is slightly longer Thus Bancroft found the period of incubation in his experimental mosquito infections to vary from five to six days Cleland, Bradley and McDonald from six to ten days and Siler Hall and Hitchens, from four to six days on the average As transmission by the mosquito is the natural method of infection, the experimental evidence indicates that the average period of incubation in dengue is from four to six days although in nature shorter and longer periods of incubation frequently are observed

Invasion — The onset of dengue usually is very sudden, but a gradual onset often is observed The patient may be apparently in excellent health until suddenly stricken or there may be vague prodromal symptoms, as lassitude slight headache and mild muscular pain, or a sense of weariness in the muscles

of the extremities There may be slight chilly sensations but a distinct chill occurs rarely Catarrhal symptoms are not present in dengue except as complications The appetite is poor and there may be diarrhea or vomiting at the onset The symptoms most complained of at this time are severe headache postorbital pain and soreness backache and pain in the muscles bones or joints especially during the first forty-eight hours of the disease There is usually much mental depression and the patient often lies in a semi stuporous condition taking little interest in his surroundings

At the time of onset the face is congested the eyes injected and it is at this time that the so-called primary eruption occurs, which some authorities regard as so characteristic of the disease Fever is invariably present, and in typical

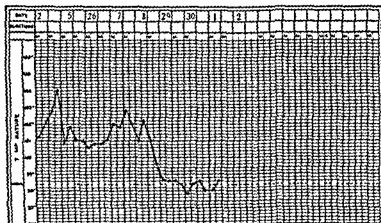


FIG 3 — Temperature Curve of Dengue Fever Natural Infection (Ashburn and Craig)

cases the temperature curve is characteristic After persisting for from twenty four to forty-eight hours the temperature generally subsides to normal or slightly above normal and may remain so but in typical cases the temperature again rises within a day or two and the saddle back temperature curve is produced which is described by all authorities who have studied the disease and which is considered very characteristic When the primary decline in the temperature occurs the symptoms disappear to reappear in slighter degree with the secondary rise in the temperature When the temperature declines, an eruption occurs in most cases which is considered as characteristic of the infection

The Fever — A rise in temperature is present practically invariably in dengue, reaching its maximum usually by the end of twenty four hours after the onset The primary rise may be to 40 5° C (105 F) or even to 41° C (106° F) but usually it does not go above 39 7 C (103 5° F) In some cases the rise in temperature is more gradual but usually the temperature reaches its height

at the end of twenty four hours after the onset and then begins to decline falling one degree or more and the so-called "period of intermission begins The decline in the temperature may be to normal or to a degree or two above normal where it remains with slight vacillations until about the fifth day after the onset when it again rises to a point almost as high as that attained during the initial rise This gives to the temperature curve the so called "saddle back" appearance well illustrated in Figure 2 On or about the sixth day after onset in typical cases there is a sudden fall in the temperature or crisis the symptoms entirely disappear and the patient becomes convalescent

It should be remembered that variations from the typical temperature curve just described occur frequently, but in the vast majority of cases the general type may be recognized even though there may be deviations from the classical picture It should be noted also that many cases of dengue occur in which the temperature remains elevated for only twenty four to thirty six hours and then falls to normal and remains so, the symptoms of the infection disappearing These mild cases often are unrecognized and undoubtedly are responsible in large measures for the rapid spread of the infection

Hyperpyrexia has been described by some authorities but is rare

The Pulse —Although there is a tendency toward a slowing of the pulse in relation to the temperature in dengue Ashburn and the writer were unable to observe the marked slowing of the pulse in this disease that is described by some writers As a rule the rapidity of the pulse increases with the temperature but this is not as marked as in many other infections although much more so than in yellow fever, in which disease the pulse is very slow as compared with the height of the temperature During convalescence in dengue there is usually a slow pulse which is often of low tension In our experience the higher the temperature and the more severe the symptoms of the infection, the more rapid the pulse rate

Skin Eruptions —It is probably true that the onset of dengue is accompanied always by an erythematous condition of the skin, but this is often so evanescent that unless it is looked for most carefully it will be missed This condition has been described by many writers as the 'primary rash' of dengue but Ashburn and the writer do not regard it as a true eruption but due to a temporary dilatation of the capillaries occurring during the initial rise in temperature It is an erythematous mottling of the skin especially upon the face neck, chest back and inside of the arms and thighs being most marked upon the exposed surfaces In many cases it resembles a deep sun burn or a scarlatinal rash and it may be present before the distinct onset of the disease and may last from only an hour or two to two or three days While this so called 'primary eruption' is very characteristic it is not diagnostic of dengue as a similar condition of the skin is noted in some other acute infections

The true dengue eruption often called the secondary rash usually appears during the third or fourth day of the disease but it may occur as early as the second day and as late as the sixth day It occurs undoubtedly in the vast majority of cases (in our experience in seventy five per cent) but as the eruption may be very slight or evanescent in character it is possible that it occurs in all cases at some time and frequently is overlooked

The localization of the eruption varies but it is most frequently observed upon the trunk It is also common on the wrists ankles neck palms of the hands and the thighs or generalized over the entire body It is observed most commonly during the final fall in the temperature but also occurs during the secondary rise and may even occur during convalescence

The character of the eruption varies greatly in different epidemics and in different individuals and macular maculo-papular measles like scarlatinal and petechial eruptions all have been noted as occurring with this infection In our experience the most common was an eruption resembling that of measles but not so dark in color and with finer macules arranged in smaller aggregations A second type frequently encountered was scarlatinal in appearance consisting of closely set or confluent bright red points but less vivid in coloring than the rash of scarlet fever Intermediate forms of the eruption occur but the two types mentioned are observed most frequently

The injection of the capillaries may be so intense especially in the scarlatina like eruptions that rupture occurs and the extravasation of blood appears as small purple dots upon the red background of the eruption Such an appearance is seen more frequently on the back and buttocks than elsewhere

The duration of the eruption varies with its intensity the most marked eruptions lasting longer than the slight eruptions In most instances the eruption is visible for about two days but it may not last longer than a few hours or again it may persist for a week A slight brownish discoloration of the skin is noted after the disappearance of the eruption in some individuals and a very fine desquamation frequently occurs which generally is overlooked In a few cases we observed a desquamation of very definite bran like scales and in one patient the desquamation consisted of large sections of the epidermis some of them an inch square and confined to the arms hands and feet

We did not observe any urticarial eruptions in the cases of dengue that we studied but intense itching sometimes occurred just prior to the appearance of the eruption Jaundice was not noted in any of our cases although it has been described by some authorities as sometimes present in this infection

Alimentary Tract — In dengue the tongue is somewhat characteristic At the beginning of the disease it is covered with a light cream colored coating which thickens and becomes darker in the middle while it disappears from the edges After the first two days the tongue usually shows a heavy yellowish central

coat with a clean tip and edges It is moist throughout the attack and does not show a tendency to fissure as in so many other fevers

The appetite usually is lost during the first two or three days of the disease but after that time is rapidly regained Nausea and vomiting sometimes occur at the onset, and diarrhea is sometimes present at this time, the stools being watery and large in amount, but blood and mucus are never present Usually slight constipation occurs which necessitates the administration of laxatives

Hemorrhages — Epistaxis is said by some authorities to be common during the onset of the infection, but we did not observe it in any of our patients nor did Siler, Hall and Hitchens in the cases that they studied Hemorrhage from the stomach and bowels has been described but was not observed in the infections we studied and it is extremely doubtful if such hemorrhages occur in dengue unless as the result of a complicating condition as ulcer of the stomach or dysentery, either bacillary or amebic Menstrual hemorrhages are observed frequently even though the patient be past the menopause The minute capillary hemorrhages into the skin, occurring during the period of the eruption have been mentioned already

Lymph Nodes — Many observers describe a general enlargement of the lymph nodes as characteristic of dengue and in the epidemic studied by Siler, Hall and Hitchens this occurred very frequently In their cases swelling of the post-cervical, epitrochlear and inguinal nodes accompanied by tenderness, was almost invariably observed, but such enlargement of the nodes does not occur always, for in the epidemic studied by Ashburn and the writer enlargement of the lymphatic nodes was not observed except in cases showing such enlargement before the onset of the infection or in those who developed inguinal adenitis from a coexisting venereal infection

No enlargement of the spleen or liver was noted in our cases although such enlargement is stated to be present in some descriptions of the disease

Articulations — Swelling of the joints especially of the knee joint is described by some writers as being frequent in dengue accompanied by the signs of inflammation In only one of our cases was such swelling noted, in this instance the wrists being markedly swollen and the skin red and inflamed Pain in the articulations frequently is present but visible signs of inflammation of the joints certainly are very unusual

Nervous System — Pain is a constant symptom in dengue but it varies greatly in distribution and in severity In some mild infections pain is slight and limited to headache twinges in the muscles and postorbital soreness while in others the pain is general and agonizing Headache and lumbar pain occur in practically all cases, and in most cases there is pain in the muscles of the arms and legs especially in the calf muscles Rarely there may be abdominal pain

Headache is most frequently frontal in location but may be post-orbital

temporal or occipital in the order of frequency named The eye balls are tender upon pressure and movement of the eye balls is more or less painful Photophobia is present in many cases

The pain in the lumbar region and in the extremities may be very severe in character and the muscles affected usually are tender upon deep pressure The tenderness is not limited to the insertions of the muscles as stated by some writers but is present in the body of the muscles especially in the muscles of the calf of the leg

While dengue is commonly called Break bone Fever patients seldom complain of any pain in the bones and it is believed that the so-called bone pains are almost invariably identical with the pain in the muscles especially if the deep insertions of the latter are involved As already stated pain in the joints is noted sometimes but intercostal pain is rare and abdominal pain still more so

A mild delirium is present sometimes during the first two days of the infection and in three of our experimental cases this occurred in one mild in type in the second slightly more severe while in the third there was marked delirium with hallucinations and hysterical symptoms Insomnia is a common symptom while the fever is high and there is much pain Meningeal symptoms have been described but are very rare in our experience

In many patients there is developed a condition of mental depression often marked during early convalescence which is most unpleasant but which gradually disappears without the production of any permanent mental disability

The Urine —Some authorities have mentioned the occurrence of albumin and casts in the urine of dengue patients but most observers are in agreement that albuminuria does not occur in dengue unless pre-existing disease of the kidney is present This is a valuable point in distinguishing dengue from yellow fever in which albuminuria with casts in the urine almost invariably occurs

Convalescence — Convalescence from dengue may be prolonged but is usually prompt and most patients improve rapidly after the temperature reaches normal Patients should not be allowed to return to work for at least four to five days after the temperature becomes normal even though they may feel perfectly able to do so owing to the danger of heart failure from a weakened myocardium

Diagnosis

In the presence of an epidemic dengue is easily diagnosed when typical but isolated cases probably would be overlooked or wrongly diagnosed The peculiar temperature curve following the sudden onset the severe muscular pains the eruption the leucopenia accompanied by an increase in lymphocytes and the shift to the left in the Schilling count render the diagnosis easy in the typical

cases, but infections occur so mild as to be unrecognizable and many cases occur in which the symptoms are atypical and easily mistaken for those of some other infection

The differential diagnosis between dengue and certain other diseases is of much importance in many regions where dengue is endemic and becomes epidemic The infections which are most important in the differential diagnosis of dengue are yellow fever malaria influenza scarlet fever, measles and syphilis

Yellow Fever —It is well known that in regions in which both dengue and yellow fever occur the two infections have been repeatedly confused, and in the United States during the periods in which yellow fever occurred in epidemic form, it frequently happened that cases of dengue were diagnosed as yellow fever or still more frequently, mild cases of yellow fever were mistaken for dengue fever According to Guiteras and Cartaya the most valuable differential features are the slower pulse the jaundice and the hematemesis in yellow fever none of which are noted in dengue In addition the absence of an eruption in yellow fever and the almost constant presence of albuminuria which is almost unknown in dengue, together with the absence of leucopenia in the blood of yellow fever patients should enable one to differentiate the two infections without difficulty

Malaria —There should be no difficulty in distinguishing between dengue and the malarial fevers if a blood examination is made, for in malaria the plasmodia usually will be found if the patient has not taken quinine In some instances a mild atypical malarial attack might simulate dengue but such an occurrence would be very unusual If the blood is negative for plasmodia in a suspected case, the administration of quinine in therapeutic doses will bring the fever to normal within three or four days at most, if the symptoms are caused by malarial infection

Influenza —In some epidemics of influenza cases occur which closely simulate dengue there being severe muscular pain distributed as in the latter infection an absence of respiratory symptoms and intense headache and mental depression but usually the respiratory symptoms which accompany influenza serve to distinguish it from dengue together with the absence of the skin eruptions which are so characteristic of the latter infection As dengue is transmitted by mosquitoes it occurs during the seasons in which these insects are present while influenza occurs most frequently in the cold seasons when mosquitoes are absent

Scarlet Fever —The skin eruption of dengue frequently resembles that of scarlet fever and many cases of infection with dengue have been wrongly diagnosed as cases of scarlet fever or scarlatina The absence of a sore throat in dengue the average age of the patients the less pronounced toxic symptoms the characteristic temperature curve and the absence of marked desquamation should serve to distinguish dengue from scarlet fever or scarlatina

Measles —A measles like type of eruption is quite common in dengue but

the absence of respiratory symptoms and of Koplik's spots and the characteristic temperature curve should distinguish dengue from measles. In addition the average age of the patients should indicate that dengue is present as measles is a disease of children while dengue affects all ages and adult cases are just as numerous as infections in children.

Syphilis. — In individual instances secondary cases of syphilis may somewhat resemble dengue but the presence of mucous patches the lesser severity of the onset the character of the skin eruption the temperature curve and the history of an initial lesion should enable one to differentiate such cases from dengue.

Other infections that have been confused with dengue are tonsillitis rheumatic fever small pox meningitis and German measles but attention to the history the physical signs and symptoms and the employment of approved methods of clinical diagnosis should render the differentiation of these conditions possible in every case.

Prognosis

The mortality of dengue is very small and it is doubtful if fatal cases ever occur except in patients suffering from some other condition which added to the dengue infection determines the fatal termination. In Australia dengue is stated to cause one death in one thousand cases 37 6 per cent of the deaths being in individuals under five years of age and 35 5 per cent in individuals over sixty years of age. In the Philippine Islands where wide spread epidemics of dengue occur a death from the infection is almost unknown.

Prophylaxis

The prophylaxis of dengue fever must be based upon the destruction of the transmitting mosquitoes or protection from the bites of these insects. The methods to be adopted in prophylaxis are similar to those used in the prophylaxis of the malarial fevers and will be found detailed in this work in the chapter entitled Malaria by the writer (Chapter XXXII Vol V).

The researches of Sabin and Schlesinger already referred to in which they were able to protect human volunteers by inoculating them with the attenuated dengue virus which had been passed through serial passages in mice offers hope that a practical protective vaccine may be developed as in the case of yellow fever.

Treatment

The treatment of dengue is purely symptomatic as there is no known specific drug which will prevent or control the infection. The vast majority of patients require no treatment beyond rest in bed the administration of a cathartic at

the onset of the disease and the administration of aspirin, if necessary, for the control of pain Calomel in small divided doses at the onset and a saline, if constipation occurs during the course of the infection, are indicated The diet should be liquid or semi liquid during the febrile period but may be quickly increased to a normal diet as soon as the temperature remains normal In patients, who suffer greatly from the muscular pains and headache, a hypodermic injection of morphine may be given, but this should be resorted to only in very severe infections when the pain cannot be controlled by other measures Rest in bed during the febrile period and for at least three to four days after the temperature remains normal should be insisted upon in order to protect the patient from a sudden failure of the circulation In patients whose temperature exceeds 103° F cold sponging is indicated, and the free administration of cold drinks as ice water or iced lemonade should be encouraged

In most cases of dengue very little treatment beyond rest in bed is indicated, together with the treatment of definite symptoms as they arise

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February 1 1947

CHAPTER XVIII A

PSITTACOSIS

By CHARLES ARMSTRONG AND DORLAND J DAVIS

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INTRODUCTION

Psittacosis is a natural disease of birds especially those of the orders *Psittaciformes* (parrots) and *Columbiformes* (pigeons) which is transmitted readily to man as an acute pneumonitis of varying severity The cause is a filterable agent now included in the psittacosis lymphogranuloma venereum group of viruses and recently classified under the family name of *Chlamydozoaceae*[1]

The term ornithosis is sometimes used to describe infections originating from birds other than the parrot group However because of the multiplicity and variations of strains of psittacosis and psittacosis like virus recovered from man and birds the older and more widely used word psittacosis, seems preferable

History

Ritter[2] gave an excellent clinical description of an acute infectious pneumonia occurring among 7 persons living in or visiting a household harboring sick parrots in Uster, Switzerland, in 1879. The name, psittacosis, was used first by Morange[3] in 1895. Since Ritter's description of the disease numerous outbreaks have been recorded throughout the world, and in 1929-1930 an extensive series of epidemics involving at least 850 cases were reported from 14 different countries. Numerous small groups of cases have been reported from time to time since this outbreak.

Etiology

It was shown by several investigators in 1930[4,5,6,7] that the causative agent was a filter passing organism present in the sputum and organs of infected persons and in the organs and discharges of infected birds. In the same year Levinthal[8], Coles[9] and Lillie[10] almost simultaneously described small coccoid bodies in the tissues of man and infected experimental animals which subsequently were shown to be the causative agent for the disease and were designated L C L bodies.

Recent studies[11,12] have demonstrated similarities of the virus causing psittacosis to the viruses causing lymphogranuloma venereum, trachoma and inclusion conjunctivitis. These viruses have similar morphology, size and staining reactions and a common complement fixing antigen although all differ in their pathogenicity for experimental animals. Both psittacosis and lymphogranuloma venereum virus show evidence of a definite cyclical development within the cells of the host[13,14]. The elementary bodies of psittacosis are approximately 200 to 300 mu in size[15], large enough to be seen through a microscope, and when stained by the Machiavello method, clusters of them are readily demonstrable in the tissues of infected animals and birds or infected chick embryos. They have not been grown on artificial media but readily grow in tissue culture and in the developing chick embryo. Intraperitoneal, intranasal and intracranial inoculation of the agent produces disease in white mice, but other commonly used laboratory animals are quite resistant to the infection. Monkeys have been inoculated intratracheally[16] with the development of a pneumonitis. The virus can be preserved for a year or longer in an active state in animal tissues held at very low temperatures (-70°C).

EPIDEMIOLOGY

Mode of Transmission—The occurrence of outbreaks of psittacosis in households harboring psittacine birds particularly newly acquired ones has been observed repeatedly as one of the epidemiological characteristics of the disease Often the suspected bird shows evidence of illness such as diarrhea ruffled feathers and nasal discharges and may die but it may appear well and yet upon laboratory examination prove to be a carrier of the virus

The virus is discharged from the infected bird in the droppings or possibly in the nasal exudates It is resistant to ordinary drying and may be suspended in the air with dust The number of cases recorded as having only remote opportunity for infection such as passing through a room containing parrots or being in a laboratory building in which the virus was being studied[17] suggest that the virus can be readily air borne

Sex and Age Distribution—Females are affected more often by the disease than males probably because the care of birds in the home more often falls to the women who are more likely to spend more time in the home than do men In the 19 9-1930 outbreak in the United States among 167 cases of known sex there were 105 females and 62 males

Adults apparently are more susceptible to infection than children and the mortality increases with age[19] During the 19 9 1930 outbreak in the United States there were 33 deaths among 169 recorded cases 19 percent all over 30 years of age In England during the same time there were 117 cases and 5 deaths 1 per cent only of which were in persons under 30 years old[8]

Incubation Period—Onset varies from 6 to 15 days after effective exposure to infected birds and usually is about 10 days

IMMUNITY

One attack of the disease probably confers at least partial immunity of long duration although data on immunity in man is meager The occurrence of inapparent but immunizing infections is suggested by the existence of bird handlers who deny a history of psittacosis but who apparently are resistant to infection from birds known to be infected The frequent presence of complement fixing antibodies in the sera of such persons and in the sera of those working with the virus in the laboratory who have not had the clinical disease also indicate the existence of inapparent infections

Pathology

Psittacosis in man is anatomically characterized by a pulmonary inflammatory process which usually progresses to a focal or lobular consolidation but may become confluent All stages of congestion and edema red hepatization and gray hepatization are seen commonly in one case The alveolar epithelial cells undergo swelling, fatty degeneration and desquamation and may be invaded by the virus, which can be seen as intracellular elementary bodies when stained with Giemsa stain Early interstitial infiltration is lacking, but a serous exudate soon appears and later is replaced by lymphocytes, large mononuclear cells and occasional mast cells The bronchioles may remain clear or may contain a sero-cellular exudate

The spleen is moderately enlarged soft and histologically shows congestion, infiltration of the pulp by lymphoid cells and an increase of phagocytes In the liver the Kupfer cells often are swollen, vacuolated and phagocytic, and focal coagulation necrosis of the parenchyma sometimes occurs[21]

Clinical Course

Clinically the disease varies considerably in severity yet presents a uniformity of symptoms suggesting those of primary atypical pneumonia except that usually the symptoms are more severe It also must be differentiated from influenza bronchopneumonia, pneumonic tularemia typhoid fever and Q fever

The onset is characterized by malaise, chilly sensations, headache and fever In severe cases the fever rises gradually with remissions, to 103 to 105 F in the second week of illness and then gradually declines for several weeks thereafter in patients who recover In mild cases moderate fever may persist for only 7 or 8 days Respirations are not appreciably increased, and the pulse tends to remain slower than might be expected from the degree of fever

Areas of pneumonitis detectable by physical signs or by roentgenograms resembling those of primary atypical pneumonia may appear early but sometimes are delayed or not demonstrable[22] On successive examinations the lesions may be seen to migrate from one part of the lung to another, and in fatal cases there is usually extensive involvement of both lungs

A dry cough often is present, and what sputum if any is produced,

is grey thick tenacious and frequently blood stained Anorexia abdominal distension and constipation are commonly present Epistaxis may occur and albuminuria is common during the height of the disease

TABLE I

Most Frequently Recorded Symptoms in 169 Cases in United States in 1929 1930

Symptom	Number of Cases in Which Present	Number of Cases in Which Absent	Unknown
Headache	11	13	44
Malaise	107	14	48
Cough	106	3	40
Chills	98	5	46
Pains other than head	95	28	46
Anorexia	9	24	53
Constipation	87	36	46
Coated tongue	85	20	64
Delirium or stupor	48	69	52
Nosebleed	5	96	48
Diarrhea	13	110	46

The leukocyte count usually is normal or slightly increased during the early part of the illness but leucopenia is the rule later In one case of our series the count on the twentieth day of illness was 600 cells per cubic mm but counts between 3,000 and 6 000 are more common

Table 1 shows the frequency of occurrence of the more common symptom as reported in 169 cases

Convalescence is apt to be prolonged and relapses are not uncommon Thrombophlebitis particularly of the femoral veins is the chief complication and is of rather frequent occurrence

Diagnosis

The recovery of psittacosis virus from the sputum or autopsy material is of course definite evidence of infection The sputum or material is emulsified in 0 85 per cent salt solution and inoculated intraperitoneally or intranasally into white mice which are observed for 7 to 10 days for

signs of illness Second and third intracranial passages of the organs of the inoculated animal will reveal the virus if present The typical clusters of elementary bodies are present in impression smears of the brain liver or spleen of infected mice, when stained by Machiavello s method Serological confirmation of the morphological identification is obtained by the preparation of yolk sac antigens for testing against a known positive serum by the complement fixation test

Satisfactory complement-fixing antigens have been prepared from La Rivers tissue cultures [3] and from the yolk sacs of infected developing chick embryos [4] Serum titers usually reach 1 32 and become higher during convalescence Since the cross fixation with serum from patients having had lymphogranuloma venereum infection may persist for some time a past history of this disease must be considered in the interpretations of the results of the test

A history of exposure to pet birds or pigeons frequently is valuable and the recovery of active virus from suspected birds is further evidence for the specific infection

Treatment

Penicillin has been shown to inhibit the growth of psittacosis organisms in tissue culture and in embryonated eggs[43] In experimentally infected mice divided doses of penicillin totaling from 1000 to 2000 units per day and continued for from four to seven days have been shown to exert a markedly protective effect when the treatment is begun early i e 1 to 17 hours after inoculation [5, 6] In man penicillin has been employed in a number of cases more or less completely confirmed by laboratory studies to be suffering from psittacosis with generally favorable results[15, 29, 8, 27, 46, 49, 0, 51] The dosages employed ranged from 10 000 to 200 000 units intramuscularly every three hours the treatments being continued for from 6 to 14 days depending upon the severity of the illness and judgment of the physician The effect of the drug is believed to be mainly bacteriostatic , therefore vigorous treatment should be begun as early as possible Treatment should be continued for several days after the temperature has returned to normal, otherwise relapses may occur

Chloromycetin[49, 53] like aureomycin[55] has been found to lessen the death rate among mice experimentally inoculated with psittacosis virus Aureomycin has been employed [4, 56, 7] with apparently beneficial results

Various sulfa compounds have been employed in psittacosis without

favorable effect in most patients[47, 48, 5] Convalescent serum is not commercially available and is of doubtful value

Prevention

Contact with sick parrots parakeets or pigeons should be avoided Frequently exposure of birds to inclement weather or starvation during shipment may activate a latent infection and birds which have been apparently well develop signs of sickness on arrival at their destination and may become sources of infection Moreover birds which appear to be perfectly well have been proved to be carriers of the virus and the source of human disease Rooms which have sheltered diseased birds or birds suspected of the infection should be disinfected thoroughly

The U S Public Health Service quarantine regulations now prohibit the importation and interstate shipment of psittacine birds for commercial purposes However shipments to zoological parks and research institutes or private shipments of not more than two birds are permitted with certain restrictions Many states and municipalities also regulate the sale and shipment of the birds within their borders

Psittacosis in Birds

The natural history of psittacosis infection among aviary bred parakeets *Melopsittacus undulatus* in California has been elucidated by Meyer[31] who found evidence that the virus carried latently is transmitted to the nesting birds during the breeding season and thus is perpetuated among the colonies Burnet s work in Australia[2] with wild birds of the psittacine family has established the fact that the infection is widespread although usually latent among these birds in their natural state as well as in captivity Many species of the family *Psittacidae* have been shown to be infected but the principal psittacine sources of human infection in the United States have been the Amazon or green parrot of Brazil *Chrysotis amazonicus*, and the common shell parakeet *M undulatus*

The infection of pigeons *Columba livia* with a virus of the psittacosis group was reported in South Africa[32] and in the United States[33] in 1940 Later the infection was related to human disease by the isolation of a virus from a flock of racing pigeons and the same virus from the lung of

a human who had been exposed to the birds and developed a fatal pneumonitis[3] More recently the virus has been found widely distributed among flocks of domestically raised pigeons of all varieties and also wild pigeons frequenting city streets and parks Nearly all cases of human disease contracted from pigeons have been traced to the domestically raised pigeons, although a few infections apparently were acquired by close contact with the wild varieties

Canaries and several varieties of finches especially the Java sparrow *Munia oryzivora*, are susceptible and may acquire the infection from psittacine birds in aviaries or stores and in turn transmit infection to man

In 1938 an outbreak of pneumonia among the inhabitants of the Faroe Islands was shown to be caused by a psittacosis like virus A widespread infection with this virus among the fulmar petrel, *Fulmarus glacialis*, which are used by the islanders as food subsequently was demonstrated[38]

Domestic chickens[3] and ducks[39] also have been reported infected and shown to be the source of human disease It is of interest that agents belonging to the same group have been found causing pneumonitis in mice[39] and cats[40] and appear to be natural parasites of these animals

Related Viruses

Several viruses morphologically and serologically similar to the typical psittacosis strains yet differing from them in their behavior in experimental animals have been recovered from patients suffering from severe pneumonitis for whom no contact with birds could be traced Eaton and associates[41] in 1941 recovered the S F strain from a fatal case in California and differentiated it from typical psittacosis virus There were 5 secondary cases, 3 nurses and 2 laboratory workers 2 of them fatal In 1943 3 strains of a psittacosis like virus were recovered from sputum and autopsy material in an outbreak of pneumonitis occurring in the bayou region of Louisiana[42, 43] There were 19 cases and 8 deaths in this outbreak No source of the virus was discovered and case to case transmission apparently accounted for all secondary cases In 1944 2 fatal cases of pneumonia were reported[44] in Chicago from which a psittacosis like organism was isolated but no source of infection was established

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July 1 1950

CHAPTER XVIII-A A

ORNITHOSIS

By HENRY A CHRISTIAN

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Introduction

Definition — Ornithosis is a psittacosis-like disease of columbidian and probably other birds and of man caused by a virus of relatively large size. Ornithosis is a word derived from ὄρνις (ὄρνιθ) a bird.

Terminology — Since 1875 a transmissible disease in birds of the psittacine species has been known and since 1879 its occurrence in man has been recognized; this has been called psittacosis, a name derived from the bird type which commonly suffers from it (for Psittacosis see Oxford Med Vol V Chapt XVIII-A). Strictly speaking psittacosis is a subvariety of ornithosis and it might well be called psittacine ornithosis in contrast to columbidian ornithosis, the disease under discussion in this chapter. With the great interest at present in atypical pneumonia or pneumonitis called also non-bacterial or virus pneumonia, ornithosis has a special interest since there is evidence that some of these patients have acquired their disease from contact with birds of both psittacine and columbidian race as well as possibly from other bird types[1-3]

ETIOLOGY

The cause of ornithosis is a virus large enough to be visible under the microscope; it is almost as large as rickettsiae[9]. The organisms have been called L C L bodies after Levinthal, Cole and Lillie who discovered them almost simultaneously; they are demonstrable in exudates, blood and organs of diseased birds and man by staining methods which demonstrate the rickettsial organism. In invaded cells appears an early matrix in which elementary bodies develop in great numbers and from which are released minute coccal bodies, M M P bodies (*Microbacterium multiforme psittacosis*). The organisms will grow freely on the chorioallantoic membrane of the chick where they produce pock like lesions or in liquid or solid media containing tissue cells. It can be transmitted to mice, guinea pigs, rabbits and rhesus monkeys; the mouse is a satisfactory and relatively safe experimental animal for the study of psittacosis and ornithosis. From spleens of infected mice and from cultures antigens can be prepared for complement fixation tests and diagnostic titers obtained from infected birds, mice and men.

It seems evident that there is more than one strain of the psittacosis virus or there may be more than one variety of virus with psittacosis caused by the psittacosis virus and ornithosis by a psittacosis-like virus, the latter of low mouse infectivity and pathogenicity, not very pathogenic for pigeons and men and producing usually in man a bronchopneumonia with very low mortality in contrast to human psittacosis with high mortality. The virus isolated from pigeons in the United States resembles closely that isolated from Australian parrakeets or cockatoos. The complement fixation test is very helpful in detecting infection in birds and making a positive diagnosis of the disease in man. Lymphogranuloma venereum, trachoma and inclusion conjunctivitis in man, Nigg's virus of mouse pneumonia and the virus of meningo-pneumonitis of Francis and Magill cause very similar complement fixation reactions and must be excluded in the evaluation of the diagnostic significance of a positive complement fixation[11]. Further investigation may develop serum reactions more specific for these several infections than the present group reactions.

ECOLOGY AND EPIDEMIOLOGY

Ornithosis is widely spread among pigeons in the United States[9]. Many of them have a latent infection or are carriers and are healthy unless some circumstance lowers resistance such as over crowding and

Etiology

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It seems evident that there is more than one strain of the psittacosis virus, or there may be more than one variety of virus, with psittacosis caused by the psittacosis virus and ornithosis by a psittacosis-like virus, the latter of low mouse infectivity and pathogenicity, not very pathogenic for pigeons and men and producing usually in man a bronchopneumonia with very low mortality in contrast to human psittacosis with high mortality. The virus isolated from pigeons in the United States resembles closely that isolated from Australian parrakeets or cockatoos. The complement fixation test is very helpful in detecting infection in birds and making a positive diagnosis of the disease in man. Lymphogranuloma venereum, trachoma and inclusion conjunctivitis in man, Nigg's virus of mouse pneumonia and the virus of meningo-pneumonitis of Francis and Magill cause very similar complement fixation reactions and must be excluded in the evaluation of the diagnostic significance of a positive complement fixation.[11,12] Further investigation may develop serum reactions more specific for these several infections than the present group reactions.

Ecology and Epidemiology

Ornithosis is widely spread among pigeons in the United States.[9] Many of them have a latent infection or are carriers and are healthy unless some circumstance lowers resistance, such as over-crowding and

other unsanitary conditions inadequate or improper feeding or infection with some other organism Pinkerton and Schwank[9] showed that pigeons on a thiamin deficient diet sickened and from them psittacosis like virus was isolated *Salmonella typhi murium* often is found complicating this virus infection in pigeons and probably this bacterium has lowered virus resistance and made a latent infection active[9] Pigeons often prove resistant to feeding or intramuscular injection of virus seemingly having developed considerable resistance from their latent infection which may have been acquired when the birds were young and caused them no observable sickness This latent inapparent infection with psittacosis like virus makes particularly difficult the eradication of ornithosis from pigeon lofts

Doves and chickens are susceptible to the virus of ornithosis and an outbreak in a chicken farm may have been initiated by a sick dove alighting among the chickens[9] In the Faroe Islands and in Iceland fulmar petrels have shown a psittacosis like virus infection in both places human infection also was found

So in the epidemiology of ornithosis it may be expected that pigeons doves barnyard fowl petrels and possibly other sea gulls may spread the disease to man[9,10] It is important then to enquire of patients with the symptoms and signs of non bacterial atypical or virus pneumonia whether they have handled or been in contact with any of these birds Already in the United States such patients have told of having handled sick pigeons one or two weeks prior to developing their symptoms Possibly droppings or urine from virus sick pigeons or other birds may have spread the infection to the human case or the virus may have been in the expired air since the sick pigeons frequently show pulmonary lesions in which the L C L or M M P bodies are present

Apparently in man as with other of this group of atypical pneumonias case to case spread of infection has taken place To prevent this those in contact with patients having atypical pneumonia or pneumonitis should wear masks and some advise wearing goggles too

Pathology

In pigeons sick with ornithosis at autopsy plastic exudates on pericardium and liver enlarged livers and enlarged spleens are found and the M M P bodies are in large numbers free or in monocytes pneumonic patches are not common in these pigeons salmonella bacteria as a rule are present also In latent infections the spleen usually is enlarged dark purplish mottled or pale and the kidneys are soft

grayish Organ emulsions from such pigeons on intraperitoneal inoculation into mice cause enlarged spleens suspensions of these spleens induce in other mice on nasal instillation focal rarely fatal pneumonia and on intracranial injection a fatal choriomeningitis with an enormous number of M M P bodies The virus has been found also in the tissues of pigeons that seem healthy and show no complement fixation test There is evidence that the cloacal content harbors the virus in such low content that the relatively non susceptible mouse fails to react there is better evidence for the infectivity of the pigeon s urine[9]

No positive statements can be made at present as to the pathological changes caused by ornithosis in man since so far no fatal cases with demonstrated ornithotic virus with autopsy have been reported Undoubtedly there will be areas of pneumonia since cases with positive complement fixation tests clinically have these lesions and from the sputum mice have been infected and probably the spleen will be enlarged as in pigeons

Clinical Course

Clinically this form of virus infection in most cases in man seems to be similar to that described for atypical non bacterial or virus pneumonia (see Oxford Med Vol IV Chapt XXVII-B) as suggested by notes on two patients observed by me at the Beth Israel Hospital in Boston The first of these (Case 1) had very slight involvement of the respiratory tract and her symptoms were those of a general infection the second of these (Case 2) in essentials was a generalized bronchitis later a bronchopneumonia

Case 1 I S female 22 was admitted to Beth Israel Hospital Sept 28 1942 complaining of mild lower abdominal pain of 3 days duration later becoming sharp and severe with diarrhea of five or six loose watery brownish movements without nausea or vomiting two days before admission she developed severe headache and fever of 102° F Shortly before admission the abdominal pain began to abate She had eaten no unusual food and those who ate with her had no gastrointestinal upset Prior to this she had been in good health Some days later on questioning she said that about 3 weeks before onset of illness she had handled a pigeon which appeared to be quite sick There had been no known contact with anyone sick

Physical examination on admission showed entirely normal conditions except for slight general abdominal tenderness lungs seemed entirely normal Blood and urine showed no abnormalities except a slight leucocytosis

13 500 and 7 700 in two counts Hinton and Kahn reactions were negative blood agglutinations for typhoid paratyphoid A and B and dysentery were negative stool cultures showed no pathogenic bacteria Temperature

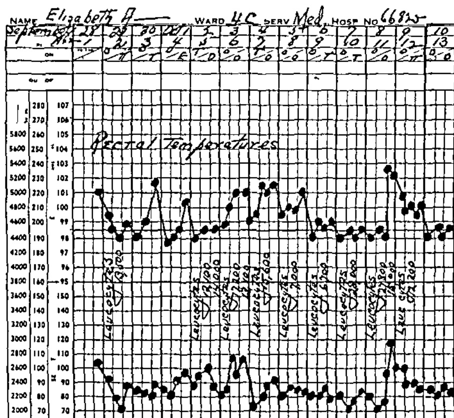


FIG 1 Clinical chart of patient with ornithosis

pulse stools etc are shown on the chart (Fig 1) X ray of chest on 9/ 9/42 showed calcified lymph nodes at right hilus no other abnormalities

On Oct 2 *pain along right costal margin with increase with inspiration* appeared and leucocytes rose to 12 000 and 14 000 rising further to 15 600 and 17 200 on Oct 3 On this day Oct 3 x ray showed cloudy haziness at the base of the left lower lung field and the temperature rose to 102 F On Oct 8 spinal puncture showed normal dynamics and normal spinal fluid Irregular rises in temperature continued

to Oct 8 after which there were very slight afternoon rises until Oct 10 X ray on Oct 15 showed normal lungs Serum taken on Oct 6 for complement fixing antibodies with psittacosis virus showed 1:2, 4 plus reaction serum taken on Oct 17 showed 1:2, 2 plus reaction The patient was discharged on Oct 23 feeling well and gaining in weight

Case 2 B S male 32 previously busied as a taxi driver was admitted to Beth Israel Hospital on Oct 20 1942 complaining of headache fever cough and malaise for 6 days At onset there was some burning pain across the central anterior upper part of his chest he slept fairly well Next day at work he developed severe headache and began to cough so he went home and went to bed After continuance of headache and severe cough with greenish sputum for two more days he

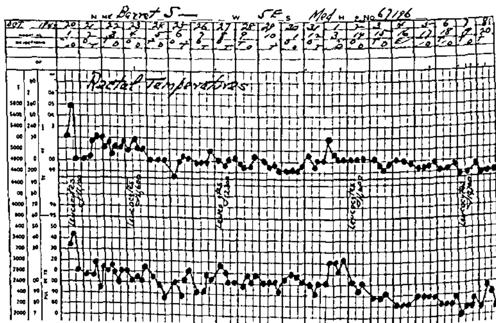


FIG 2 Clinical chart of patient with ornithosis

found he had a fever of 102.4° F The next night and the following day he was sweating as his fever continued he was sent to this hospital with the diagnosis of bronchopneumonia The patient stated that about 2 weeks before his illness he had been feeding pigeons out of his hand a thing that he had done only very rarely

Physical examination on admission showed considerable dyspnea with a grunting respiration and moderate cyanosis His temperature (see

Fig 2) was 104 8 F by rectum with respiratory rate 38 Pharynx was reddened uniformly Lungs showed rhonci throughout with showers of medium expiratory rales most marked in left basal region where very slight dulness was made out Otherwise physical examination showed no abnormalities Blood was normal except for slight leucocytosis 11 100 Sputum by smear and culture showed no predominating bacteria X ray on Oct 20 was unsatisfactory but showed no evidence of pneumonic consolidation Pulmonary physical signs were essentially the same with gradual decrease in rales X ray on Nov 4 showed enlarged left hilar shadow and an irregular increase in markings in lower lung fields on both sides more on the left Temperature fell to normal on Nov 1 and patient went home on Nov 10 essentially recovered from his acute illness Serum of Oct 31 gave a negative complement fixing reaction for psittacosis antibodies

Diagnosis

Presumptive diagnosis can be made in a patient who following handling a sick appearing pigeon dove barnyard fowl duck[14] petrel or possibly other sea gull develops a febrile disease similar to that described in the previous section Positive diagnosis can be made by inoculating the sputum into mice and then finding the characteristic organism or obtaining a positive complement fixation test[8 1] Possibly the organism may be demonstrated in sputum from the sick patient

Prognosis

So far in man ornithosis has had a very low possibly of itself no mortality

Treatment

Aureomycin has been reported to give very satisfactory therapeutic effects in the closely related disease psittacosis and seems to be equally effective in ornithosis[1 16 17] although so far it has not been used in many patients with a positive diagnosis of ornithosis It is recommended to be used in the way discussed in the chapter on Non bacterial Pneumonias Vol IV Chapt XXXII B Aureomycin seems preferable to sulfadiazine or penicillin formerly recommended chiefly on the basis of preventing secondary bacterial infection Incidentally aureomycin can be expected to act against the most probable secondary bacterial infections as well as having an effect on the organism causative of ornithosis In addition to the use of aureomycin treatment should be the same as that described for Non bacterial Pneumonias

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July 1, 1950

CHAPTER XVIII-B

FOOT-AND-MOUTH DISEASE

By MAJOR JAMES STEVENS SIMMONS Medical Corps U S Army

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Definition — Foot and mouth disease is an acute highly contagious febrile disease caused by a filterable virus and characterized by a vesicular eruption or the mucous membrane of the lips and mouth and on the skin of the extremities It is of considerable economic importance because of its extensive epidemic occurrence among cloven hoofed animals including cattle sheep pigs and goats Reindeer and camels are susceptible and it has been claimed that dogs cats and other animals may be attacked While primarily an affection of lower animals this disease is also of interest in human medicine because of its occasional appearance in man As a rule the death rate is low both in lower animals and in man but a malignant form may occur in cattle and goats Several immunologically distinct types of the virus have been demonstrated Recovery from an attack of the disease is followed by immunity against subsequent infections with the same type of virus but not against the others

Synonyms — The following names have been applied to foot and mouth disease aphthous fever epizootic aphtha aphthae epizooticae infectious aphtha eczema contagiosa fievre aphtheuse cocotte (French) Maul und Klauenseuche (German) and febre aftosa (Italian)

V 1 V 933

History and Distribution

For several centuries foot and mouth disease has been recognized as a menace to cloven hoofed animals especially in Europe. Its contagious nature was noted in 1764 by Sager who studied the disease in Norway but prior to the last century the condition was commonly attributed to atmospheric and climatic conditions or to various other causes including food poisoning.

It appears that for some time foot and mouth disease has been endemic throughout the world and from time to time destructive epidemics have occurred in most countries. The last extensive European epizootic which began in 1887 started in Russia and spread over all of Europe, the disease has not yet been eradicated. In Germany the years of highest incidence have been 1891, 1899, 1911 and 1919. During 1911 (Hutyra and Marek 1926), the disease affected 3 355 369 cattle, 2 555 731 hogs, 1 602,927 sheep and 53 674 goats or about one seventh of the animals in that region. Severe outbreaks causing great economic losses have also been reported in most of the other European countries including Denmark, France, Holland, Austria, Hungary, Switzerland and Italy. In Great Britain the disease has continued to appear annually since 1900 in spite of the fact that since that year the importation of living cloven hoofed animals from the continent has been prohibited. There were 1,854 separate outbreaks in 1923 resulting in the slaughter of 125,098 animals. The continued appearance of the disease in the British Isles, after the importation of hay and straw had been prohibited, led to the suspicion that the infection might have been introduced by birds from continental Europe. It is claimed that in Great Britain the disease is usually mild, with a mortality of only 2 to 3 per cent while on the continent it may occur in a malignant form causing a mortality as high as 50 to 70 per cent.

Foot and mouth disease has appeared in the United States on several occasions during the last sixty years (Mohler 1915). In 1870 the disease was introduced into New England from Scotland by way of Canada. Ten years later the condition was recognized in several lots of cattle during their importation into this country. In 1884 its introduction in infected cattle caused an outbreak at Portland Maine. Subsequent to the formation of the United States Department of Agriculture this agency enforced the inspection of all imported cattle. Outbreaks occurred in 1902 and 1908 which were ascribed to the use of contaminated cowpox virus obtained in Japan. In the extensive epidemic, which began in Michigan during 1914 it was suspected that the virus had been introduced with merchandise from South America. At that time the infection spread to twenty two states and to the District of Columbia, resulting in the slaughter of 3 556 herds valued at about $6 000 000. In 1924 the disease appeared in California and was presumably imported in garbage, used as food for

hogs During 1924 and 1925 outbreaks of undetermined origin occurred in Texas, but as in many preceding epizootics, these outbreaks were suppressed immediately by slaughter of the infected and exposed herds

Etiology

Foot and mouth disease is caused by an ultra microscopic, filterable virus As with other infections many different bacteria and protozoa have been suspected as the etiological agent However the experiments of Loeffler and Frosch (1898) proved that the virus is invisible and that it will pass through the pores of Chamberland or Berkefeld filters This observation which has been confirmed by many investigators was the first discovery of a so-called ' filterable virus capable of infecting animals

The virus may be demonstrated in the vesicular fluid saliva urine milk and blood of diseased cattle during the febrile period but after 3 to 6 days the lesions are no longer infective Olitsky Traum and Schoening (1927) emphasized the importance of using fresh vesicular material not more than two days old for the diagnostic inoculation of animals

It has been shown by Olitsky and Boez (1927) that the infective agent can pass through Berkefeld V and N candles Chamberland filters with pores as fine as the L 5 type Seitz filter disks collodion membranes and Bechhold s ultrafilter They estimated the size of the virus at between 20 and 100 millimicrons in diameter and reported the iso-electric point to be about pH 8 At pH 6 6 to about pH 8 the virus carried a positive charge and at pH 8 11 the charge was negative However Burbury (Maitland 1930) found that from pH 6 6 to pH 9 4 the virus was negatively charged

In spite of a few unconfirmed claims it is believed that the virus has not yet been cultivated on lifeless artificial media The optimum reaction for its preservation is pH 7 5 to 7 6 (Bedson and Maitland 1925 Stockman and Minett 1926 Olitsky and Boez 1927 Schoening, 19 7) and it is destroyed by slight changes in alkalinity or acidity, as for example during the souring of milk It may remain infective for long periods if kept at pH 7 5 in 50 per cent glycerol

When suspended in salt solution the virus is killed in a short time by exposure to sunlight or ultraviolet rays or by certain chemicals including chlorine iodine potassium permanganate formaldehyde sulphuric acid or caustic soda Ox bile and many of the aniline dyes are weakly destructive, and phenol has a very low viricidal action It was shown by Loeffler and Frosch (1898) that the virus can live for at least five months in 1 per cent phenol It is also very resistant to the action of alcohol (Stockman and Minett 1926 Bedson and Maitland 1925 Abe 1925) chloroform (Stockman and Minett

1926 Bedson and Maitland, 1925, Bedson, Maitland and Burbury, 1927) and to ether (Schmid, 1926) Olitsky and Boez (1917) observed that virus is especially resistant to chemicals which coagulate protein and suggested that the coagulum protects the virus They recommended sodium hydroxide or antiformin as disinfecting agents

The virus is affected by heat according to laws that apply to the destruction of bacteria (Burbury 1928) and is killed in 20 minutes at 50° C, or in 10 minutes at 70° C Pasteurization is sufficient to kill it in milk (Hull, 1930) It is resistant to cold and may resist alternate freezing and thawing at least twenty times, it may remain infective for 433 days even when kept at ±5° C (Bedson, Maitland and Burbury, 1927)

The effect of drying has been studied extensively, because of its possible importance in the natural transmission of the disease It is claimed (Topley and Wilson, 1931) that when virus is dried rapidly on a glass slide at 37° C, it may become inactive immediately, but if dried slowly at room temperature, it may survive for at least six months The experiments of Burbury (1928) indicate that destruction of the virus in the dried state is caused by chemical activity due to the presence of moisture, and that certain materials including hay bran, flour sugars and cow hair, favor the survival of virus dried on them for periods long enough to implicate some of them as conveyors of the infection It has been observed by Trautwein (1926) that in vesicle tissue, virus remained infective after 67 days exposure to outdoor atmospheric conditions in winter Schoening (1927) found that when dried on hay or in garden soil and kept under field conditions, virus remained infective for 25 to 30 days

Two types of virus, 'A" (Allemand) and O" (Oise), were distinguished by Vallee and Carre (1922) Both types are equally infectious for animals and produce identical clinical symptoms in cattle, pigs, sheep and guinea pigs However, they can be differentiated by their failure to produce cross immunity Animals that have recovered from infection with one type are immune to reinfection with the same type, but can be infected with the other type In 1926 Waldmann and Trautwein discovered another immunological type designated as 'C' It has since been observed that these three types, A, O and C are widely disseminated, but have an irregular geographical distribution Ciuca (1929) claims that the three types of virus may be differentiated by the complement fixation test

Pathogenicity

In naturally susceptible animals including cattle, hogs sheep and goats, foot and mouth disease can be produced by local application of the virus to the scarified mucosa of the lips or mouth If the material is inoculated intramuscu

larly, larger doses are required The buffalo American bison, camel chamois llama giraffe antelope and other cloven footed animals as well as marmots and hedgehogs, are also susceptible and may suffer from natural outbreaks of the disease

In certain other animals including mice dogs, cats and ferrets and in fowls ducks and other birds, experimental inoculation of the virus may fail to cause infection or may produce insignificant local lesions in a small proportion of *individuals Rats and rabbits have been found susceptible to artificial inocu*lation, but it appears that these animals are probably too resistant to be of great importance in the natural spread of epidemics

Because of its susceptibility the guinea pig is a valuable animal for diagnostic and experimental work (Hecker 1899 Waldemann and Pape 1920 1921 Hobmaier 1921, Cims and Fortner, 1924) After intracutaneous or subcutaneous inoculation of virus into the pads of the fore and hind feet the infection appears within 12 to 96 hours There is a rise in temperature accompanied by swelling and redness of the foot followed by the development of small vesicles about the point of inoculation These coalesce resulting in a large blister which covers the entire sole of the foot and may contain as much as 0 1 c c of fluid This fluid contains the virus in such concentration that when diluted as much as 1 1 000 000 it may infect normal guinea pigs Usually the animals show signs of general illness and secondary vesicles appear on the uninoculated feet lips gums and tongue After about two days these lesions become grayish white and flattened and after this they dry slowly and disappear in 10 to 14 days *The virus is demonstrable in the blood until the secondary vesicles* develop but it is never as concentrated as in the vesicle fluid In guinea pigs the mortality is about 5 per cent and it has been suggested that death usually is due to the activation of some latent infection The disease can be produced by intramuscular, intraperitoneal or intravenous inoculation but when virus is introduced by these routes, larger doses may be required and the appearance of vesicles may be slightly delayed There is no evidence to indicate that experimentally infected guinea pigs can transmit the infection to normal animals by natural contact Animals that have recovered from the infection are highly resistant to subsequent injections of the same type of virus

TRANSMISSION

During epidemics in herds of cloven hoofed animals foot and mouth disease is probably most commonly spread by direct contact The highly contagious virus present in the vesicles saliva urine and milk during the early stage of the disease readily *causes infection when it comes in contact with the mucosa of the* mouth nose or conjunctiva or with the abraded skin of normal susceptible animals

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There is considerable evidence to indicate that inanimate objects may be of importance in the transmission of infection In the carcasses of infected animals the virus soon disappears from muscle tissue because of the increase in acidity with rigor mortis but it may persist in the bone marrow for 42 to 76 days and in the blood for at least 34 days In milk the virus is supposedly destroyed by fermentation during the manufacture of cheese but additional experimental studies are required on the survival of virus in milk under various conditions

In manure virus is usually destroyed in a few days (Minett 1928) due to the heat generated or to changes in reaction However Wagener (1928) has referred to outbreaks that might have been due to infected manure In manure left in the open virus has survived 59 days at the surface of the stack He also showed (1927) that virus may survive in sewage during the summer (17 to 21° C) for 14 to 21 days in the fall (13 to 18 C) for 43 to 49 days and in winter (4 to 13° C) for 103 to 104 days It has been observed (Lebailly 19 2 Vallee and Carre 1922) that even without disinfection the infectivity of dung and of materials in stables is soon lost Experiments by Trautwein (1926), Schoening (19 7) and Burbury (1926) show that, when dried on such foods as hay bran flour or other materials including hair or clothes the virus can remain alive and infective for periods long enough to implicate these materials as potential factors in the transmission of the disease

PATHOLOGY

Post mortem examinations of animals that have died of foot and mouth disease or have been slaughtered during the development of the infection usually show the characteristic vesicular eruption an acute catarrhal swelling of the mucous membrane of the mouth and respiratory tract and less frequently minute hemorrhages on serous membranes especially the visceral layer of the peritoneum In some cases vesicles or ulcers may be present on the mucous membranes of the respiratory tract and the intestinal tract the spleen may be moderately enlarged and soft the pericardial sac may contain fluid and in 2 per cent of cases the heart valves are oedematous In malignant cases (McKinley 19 9), the heart muscle may show acute inflammation with hyaline degeneration and in prolonged cases may show evidence of necrosis and connective tissue regeneration Such changes have been considered as a myolytic process caused by a specific toxin

Maitland (1930) has described the histology of the characteristic vesicles of foot and mouth disease as follows The earliest histological lesion consists in *degeneration and necrosis of small foci of epithelial cells* comprising at first only a few cells The protoplasm is ballooned the nuclei are swollen or pyk

The apparently spontaneous appearance of the disease in herds protected from direct contact with infected animals may be due to a variety of factors. While the virus usually retains its pathogenicity only for a few days in the infected animal, it can survive for relatively long periods under other environmental conditions. It was once considered possible that a large proportion of recovered animals might become chronic carriers of the virus and there is some epidemiological and experimental evidence in support of this belief. Outbreaks have been attributed to contact with animals that had recovered from the infection eight months to one year previously (Olitsky, Traum and Schoening, 1928), and virus has been demonstrated in healed lesions on the feet of animals eight weeks and 251 days after their acute infection (Assel, 1913, Von Bohm, 1913). However, after reviewing the literature Brandt (1928) concluded that carriers are less common than was formerly supposed and this view is held by many other investigators (Schoening 1927, Waldmann and Reppin, 1927, Trautwein, Thomashoff and Hove, 1928, Lebailly, 1926). It has also been suggested that infective virus may be carried mechanically by animate beings including insects, birds, horses, dogs, rodents and man, or by contaminated inanimate materials such as carcasses, milk, hay, bran, litter, drinking water, clothes or other objects. In a few outbreaks biological products including smallpox vaccine and the virus and anti-serum of hog cholera prepared from animals infected with foot-and-mouth disease, have been responsible for dissemination of the latter condition (Mohler and Rosenau, 1909, Mohler, 1924).

Experiments with the common house fly, a stable fly, Stomoxys calcitrans (Lebailly, 1924), the bed bug, Cimex lectularius (Arkwright and Burbury, 1925), and the cattle tick, Margaropus annulatus (Mohler, 1926), have failed to incriminate any of these insects as intermediate hosts. However, Mohler (1926) demonstrated virus in ticks removed from animals in the febrile stage of foot-and-mouth disease and suggested the possibility of its transmission through the eggs to the seed ticks and in this way back to cattle. This has not been proven.

There is no direct indication that birds may be a factor in spreading the virus, and while certain rodents and other animals including horses and dogs are slightly susceptible to experimental infection, their relative resistance indicates that, except as mechanical carriers of virus, they may not be of importance in the natural dissemination of foot-and-mouth disease. Olitsky, Traum and Schoening (1928) believe that man is next in importance to infected animals as a factor in the spread of the disease, and that generally he carries the virus mechanically on his clothing or person. From epidemiological studies Kling and Hojer (1926) suggested that the virus might persist on the nasopharyngeal mucosa of human beings who are healthy carriers, but this suggestion has not yet been confirmed experimentally (Waldmann and Trautwein, 1928).

and feet There is a loss of appetite and the eroded areas left by the rupture of the vesicles in the mouth are painful and interfere with the mastication of food The animal stands with a staring expressionless appearance saliva dropping in long sticky threads from the corner of its mouth

The vesicles may also appear on the muzzle and more rarely around the base of the horns on the nasal mucosa or on the conjunctiva. It is not unusual for large vesicles to develop on the teats and udder Often within a few hours after the beginning of the disease there is swelling redness and tenderness of the skin of the coronary band the heel of the foot and the interdigital space Within two days the small vesicles usually increase in size and may become as arge as a hazel nut They are filled with a clear fluid which later becomes cloudy After rupture the walls of the vesicles become dry forming brown crusts This involvement of the feet causes pain and is responsible for the lameness and the stiff gait which are characteristic early signs of foot and mouth disease Secondary bacterial invaders may infect the lesions on the feet udder teats or other parts of the body but usually the lesions heal in 10 to 14 days and there are no complications Commonly the mortality is low from 0 1 to 5 per cent but malignant outbreaks with death rates as high as 60 and 80 per cent have occurred among cattle and goats in central Europe In this severe form of the disease death is more frequent among the younger animals and appears to be due to gastroenteritis and endocarditis During the stage of apparent recovery often about the fifth or sixth day the animal suddenly becomes weak and apathetic stops eating grinds its teeth has difficulty in breathing drops to the ground and dies in a short time

In general the symptoms produced by foot and mouth disease in hogs sheep and goats are similar to those observed in cattle but the infection may be less severe

Foot and mouth Disease in Man — While man is less susceptible to foot and mouth disease than the cloven hoofed animals human infections have been reported during many of the European epizootics of the last century According to Hutyra and Marek (1926) the infection is mostly transmitted by raw or insufficiently heated milk from affected cows or by whey (Dieckerhoff) cheese and butter (Schneider Frick Frohlick) prepared from such milk In rare instances persons engaged in work around the infected animals may contract the di ease by direct contact with the affected parts of the body as in milking slaughtering or during treatment of the patients Bussenius and Siegel in 1896 collected records of more than 1 500 human infections supposedly due to this disease They reported sixteen epizootics between 18/8 and 1896 during which in certain instances entire households and even townships became affected In three outbreaks 36 23 and 16 fatal cases respectively were re ported Arkwright (1928) who reviewed the subject of infection in man sug

notic Polymorphonuclear leukocytes are present in small numbers in the earliest lesions The process of epithelial necrosis spreads laterally and to some extent throughout the thickness of the epithelium, associated with larger numbers of polymorphonuclear leukocytes As the lesion advances, polymorphonuclear infiltration and increased vascularity become prominent in the sub epithelial tissue In this area there is also endothelial proliferation in varying degrees Separation of the epithelial layer gives rise to a small cavity, an early vesicle, which when fully developed is covered by the stratum lucidum and a thin layer of underlying cells and has for its base isolated areas of the stratum germinativum The margins of the lesions show a rather sharp transition to normal tissue The covering usually ruptures and restoration proceeds by the proliferation of the islands of epithelial cells left in the base of the lesion" It has been suggested by Maitland (1930) that excepting the typical vesicles, many of the other pathological lesions observed may be due to secondary infection of the ulcers left by broken vesicles, and that this may even account for the sudden death in the so called malignant form of foot and mouth disease

There is some question as to whether inclusion bodies are formed in foot and mouth disease In 1908 Terni (McKinley, 1929) described a small protozoan like body (cytorhyctes) in the vesicular fluid and internal organs of over four hundred infected cattle Gins (192?) described intracellular bodies 1 5 microns in diameter in lesions on the tongues of infected guinea pigs, but their significance remains in doubt since Trautwein (1925) found similar bodies in lesions produced by heat or acid and concluded that they were not specific Ruhle (1926) has reported bodies similar to those observed by Gins, in epithelial cells from the tongue of normal guinea pigs and cattle Therefore, we may conclude that there is no proof of the existence of specific inclusion bodies in foot and mouth disease

SYMPTOMS

Foot and mouth Disease in Domestic Animals — In naturally acquired foot and mouth disease in cattle the time required for incubation is usually from 2 to 4 days but in exceptional cases the period may be as long as 11 days The disease begins with fever which is more pronounced in young robust animals During the first two days the temperature may reach 41–42 °C, and this is usually accompanied by some acceleration of the pulse rate The fever decreases as soon as the local lesions develop and except in cases with secondary bacterial infections is rarely a feature during the remainder of the disease

The other symptoms vary according to the location of the characteristic vesicular lesions Within 12 to 72 hours after the beginning of the fever small blisters usually appear on the mucosa of the tongue lips gums, hard palate

lows After a short incubation period the disease begins The onset is abrupt with mild fever which may be accompanied by a sensation of heat and dryness in the mouth painful swallowing and vomiting This usually is followed within 2 to 4 days by the appearance of vesicles on the mucous membranes of the lips and mouth on the palms soles and around the nails but in some cases vesicles are not found in all these locations They may be as large as peas In some cases they develop along the borders of the tongue and rarely on the conjunctiva or the skin of the face There may be some salivation and diarrhea The fever usually subsides when the vesicles have developed and these lesions recede rapidly and heal in a short time

While the disease usually is mild and rarely is fatal in adults the clinical reports indicate that in frail children it may cause an intestinal catarrh resulting in death It is generally believed that man rarely contracts foot and mouth disease (Olitsky Traum and Schoening 1927 Maitland 1930) but additional investigations will be required to determine the real incidence and importance of this infection

Diagnosis

During the course of an epizootic typical cases of foot and mouth disease may be recognized or suspected by observation of the characteristic symptoms However with atypical or sporadic cases and especially with cases seen at the beginning of an outbreak the diagnosis should be established by the inoculation of infective material into other animals It is necessary to rule out all other inflammatory conditions which affect the tissues of the mouth and feet of cattle hogs sheep and other susceptible animals but the disease most likely to cause serious confusion is the so-called vesicular stomatitis of horses Vesicular stomatitis which occurs in the United States and South Africa is primarily a virus disease of equines but cattle may become infected under natural conditions The vesicles resemble those in foot and mouth disease but are less extensive and rarely affect the feet or other parts of the body The two viruses may be differentiated by the inoculation of non immune cattle and horses and by specific immunity tests When injected intramuscularly in cattle the virus of vesicular stomatitis fails to produce lesions while similar injection with foot and mouth virus causes typical infection However when the virus of vesicular stomatitis is inoculated in the scarified tongue of a horse it produces lesions while the virus of foot and mouth disease fails to do so Hogs may be infected with the virus of vesicular stomatitis experimentally but they do not contract the disease under natural conditions Guinea pigs are susceptible to the viruses of both diseases and as there is no cross immunity between them a series of these animals immunized against the various types of foot and mouth virus

gested that some of the milk borne epidemics may have been due to bacterial infections rather than foot and mouth disease He stated that Lebailly in 1921 investigated ten human cases of aphthous stomatitis, believed to be foot and mouth disease contracted through drinking milk, and that in three instances he failed to transmit the infection from man to cattle, and consequently expressed doubt as to the possibility of human infection However, there is evidence to indicate that this disease does occur in man McBride (1896) reported cases in which the evidence is convincing, and Arkwright mentions a veterinary surgeon who accidentally infected himself while examining an animal, adding that Bertarelli in 1908 reported two cases acquired by direct contact with animals, and in one instance succeeded in transferring the infection to a calf, and that Favero transmitted infection from a human case to a calf

Many of the reported cases occurred before the susceptibility of the guinea pig was discovered and their diagnosis has been questioned as unconfirmed by modern diagnostic methods including the reproduction of the disease in susceptible animals and the identification of the virus by specific immunity tests

The case of Pape (19 1) who was accidentally infected in the laboratory, furnishes an excellent example of foot and mouth disease in man While collecting virus from a pig this investigator cut his thumb on a broken glass vessel Two days later he became ill with a slight headache and chilly sensa tions On the third day vesicles appeared on the palms of the hands and soles of the feet, and during the next two days other lesions developed in these two locations The size of the vesicles varied from the diameter of a flax seed to that of a cherry stone, they contained clear fluid and healed rapidly without suppuration No buccal lesions were observed except a slight swelling and tenderness of the gums This case occurred before Waldeman and Pape (1921) discovered the diagnostic value of the guinea pig and consequently the diag nosis was unconfirmed by animal inoculation Pape was later shown to be immune to inoculation with foot and mouth virus In 1922 (Arkwright, 19 8) during an epizootic of foot and mouth disease in Como, there were several hu man cases of vesicular stomatitis in some of which the vesicles also appeared on the hands With clear vesicular fluid from one case, Pancera (192) in Milan reproduced the disease in a calf and in guinea pigs Gerlack (1924) re ported infection in his five year old daughter, which followed two days after eating whipped cream and butter The diagnosis was confirmed by trans mission of the virus to guinea pigs Trautwein (1929), who has reviewed the subject, records an undoubted human case confirmed by guinea pig inocu lation and serial transmission of the infection in these animals From the records of cases such as those reported by Pape (1921) Gerlack (1924) and Trautwein (1929), the symptoms of foot and mouth disease in man are as fol

the disease is recognized, a quarantine is established and maintained until certain tests indicate the virus no longer exists in the infected premises Such tests which are made 30 days after the cleaning and disinfection consist in placing a few normal animals on the previously infected premises which are then gradually restocked if no infections occur In Great Britain the methods used for prevention are somewhat similar to those employed in the United States However many countries of continental Europe rely mainly on isolation and treatment rather than the slaughter of infected and exposed animals Human infections may be prevented by avoiding contact with contaminated materials Pasteurization destroys the virus in milk and milk products Persons whose occupations bring them in contact with infected animals may protect themselves by observing the ordinary rules of personal hygiene When leaving infected premises they should disinfect their clothing in order to avoid spreading the virus to other locations

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and against vesicular stomatitis virus, may be used for determining the specific nature of the infection

Treatment

There is no effective specific therapeutic agent available, and the treatment usually consists in attempts to allay the local inflammatory lesions and to prevent secondary bacterial infection Hyper immune serum and convalescent serum have been used but they appear to be of little value except that when administered early in the disease they may decrease the severity of the lesions However when used prophylactically, serum produces a passive immunity and protects cattle against contact infection for five to eight days

A great number of chemical compounds have been studied (Waldmann, 1928 Jacob 1926 Steinhoff 1927, Gins, 1924, Saxinger, 1924, Kraus, 1926, Walker and Taylor, 1926, Maitland, 1928), and while a few appear to have some beneficial action no specific has yet been found

Prevention

While methods are available for producing either active or passive immunity to foot and mouth disease, the preventive measures usually employed depend on the protection of herds from exposure to infection

Animals that have recovered from the disease are resistant to inoculation with the same type of virus for 6 to 12 months Serum from such immune animals will neutralize the homologous virus in vitro and when injected into susceptible animals will protect them against infection for several days Such anti sera either alone or combined with a weak virus have been used for the prevention of infection The former method results in temporary immunity, and the latter is dangerous as it produces a mild infection Formalized vaccines (Valles Carre and Rinjard 1925 1926) have been used successfully for the active immunization of guinea pigs and heifers and may prove to be of value for general use

In the United States precautions are taken to prevent the importation of virus, and during epizootics the following control measures are employed All infected and exposed animals are slaughtered and the bodies are either burned or buried The contaminated premises are then thoroughly cleaned and treated with a disinfectant While there has been some doubt concerning the viricidal effectiveness of many disinfectants certain substances including lime, chloride of lime bichloride of mercury saponified cresol solution and formaldehyde are supposedly of value Olitsky, Traum and Schoening (1928) advocated for such disinfection a 1 or 2 per cent aqueous solution of sodium hydrate As soon as

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CHAPTER XVIII-C

SWINE FEVER

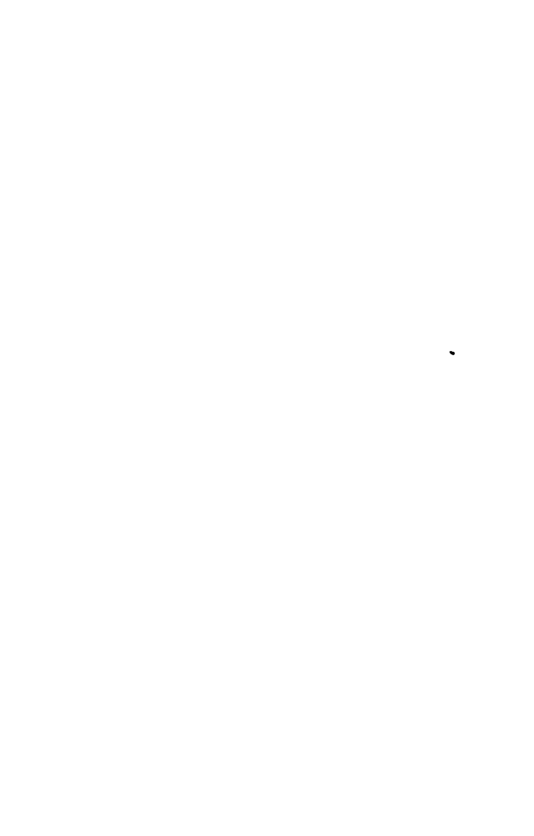
By MAJOR JAMES STEVENS SIMMONS Medical Corps U S Army

Synonyms Hog cholera cholera suum pestis suum pest porcine Schwein pest (virus schweinpest) peste porcina and Schweindifteritis

Swine fever or hog cholera is an infectious septicemic disease of swine caused by an ultramicroscopic filterable virus as shown in 1903 by de Schweinitz and Dorset[1] It is characterized by an acute febrile reaction with conjunctivitis an eruption of the skin nasal discharge vomiting, constipation followed by diarrhea and extreme weakness In the acute cases which die in 3 to 8 days there are signs of a hemorrhagic septicemia the lesions of which are especially pronounced in the intestinal mucous membrane In more chronic cases there may be ulcerative and necrotic lesions in the large intestines In the past there has been much confusion concerning the classification of hog cholera due to the fact that infection with the virus of this disease is often complicated by secondary infections with certain bacteria commonly present in apparently healthy swine Thus Salmonella suipestifer or other organisms of the paratyphoid group are frequent invaders producing secondary necrotic intestinal lesions and the so-called button ulcers and Pasteurella suiseptica, the organism of swine plague may likewise cause pneumonia or other complications At first it was thought that the disease was caused by Salmonella suipestifer (Salmon and Smith 1885)

Because of its wide distribution and its tendency to occur among swine in extensive epizootics with a high average mortality hog cholera is of considerable economic importance The disease appears to be limited to swine all ages and breeds of which may be infected but young animals of highly bred stock are most susceptible Wild pigs may contract the disease (Kitt 1916 Bornemann 1923 Gerlach 1926) The following animals have been resistant to experimental inoculations the mouse guinea pig rabbit cat sheep goat cattle donkey horse dog goose hen duck and pigeon Hog cholera appears to be of no direct importance in human medicine as it is claimed that man is not susceptible to infection with the virus or with the secondary invader Pasteurella suiseptica

Hog cholera or swine fever however does have an indirect importance in human medicine since the natural disease in hogs may be the source of human



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infection with one of the bacteria (Salmonella suipestifer), so usually associated with the virus in the disease in hogs resulting in a form of food poisoning Numerous instances of this have been reported Examples are cases reported by Gill[3] Shaw[4], Bauer and McClintock , Clayton and Milne[6] and Krumwiede, Provost and Cooper[7] Stewart and Litterer[8] reported one outbreak involving 150 persons Usually the organisms or toxins formed by them cause in a few hours after eating the contaminated food vomiting, abdominal pain, marked diarrhea and severe prostration In a number of cases death has resulted Bullowa[9] has reported a patient with pneumonia and gangrene of the lung apparently due to this organism It is possible that some of the cases considered as paratyphoid fever actually are infectious with Salmonella suipestifer

Treatment is the same as for other bacterial food poisonings, there is no specific serum available

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CHAPTER XVIII-D

RIFT VALLEY FEVER

By FREDERICK R TAYLOR

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Synonym — Enzootic hepatitis applicable only to the disease in certain animals as others fail to show marked hepatitis At times it may become epizootic within limited geographic areas

Definition — Rift Valley fever is an infection due to a filtrable virus which affects chiefly sheep and cattle in certain parts of East Africa and which is transmissible to man and to certain other mammals A number of mammals however are insusceptible

HISTORY ETIOLOGY EPIDEMIOLOGY AND IMMUNOLOGY

The history of our knowledge of this disease is interwoven so closely with studies on its etiology epidemiology and immunology that these several phases of the subject can be discussed together profitably

In July 1930 the Veterinary Research Division of the Department of Agriculture in Kenya Colony East Africa was asked for aid in diagnosing a disease that was killing large numbers of newly born lambs on a farm of about 30 000 acres in the Rift Valley where sheep had been raised successfully for several years Later in June before lambing had started there were many unexplained abortions among the ewes in the several flocks on the farm Early in July 60 out of 80 lambs in one flock died

at the age of from 3 to 7 days most of them when 3 days old The day before death they were listless, weak and disinclined to feed Along with this disease in the lambs there was a marked rise in mortality among the ewes on the farm and abortions increased in practically all the flocks The ewes were found dead or were observed to be ill for only a few hours before death The sick ones showed a thick mucopurulent nasal discharge some vomited and exceptionally the stools would consist of practically pure blood Most of the ewes that aborted were not visibly ill at the time Within a few weeks the lambs in all the flocks were affected and about 3 500 lambs and 1 200 ewes had died though abortions had ceased By this time it was known that the same disease was affecting both lambs and ewes being hyperacute in the former and that abortion usually followed recovery of a pregnant ewe from the disease. The flocks then were moved to an adjoining farm at a higher altitude and after 5 or 6 days no further cases developed though the disease continued for several months among experimental control animals left on the lower farm

The above data were reported by Daubney Hudson and Garnham who were engaged in investigating the outbreak and who showed that the disease was inoculated readily by injecting blood from a sick animal into a healthy one When death resulted it was usually on the 3rd or 4th day after inoculation Those animals which survived often recovered in less than a week though some improved and got worse again The liver as well as the blood was found to be rich in the infecting agent Experiments showed the disease to be due to a filtrable virus Exceptionally rams were infected naturally Sheep cattle, goats and man were found susceptible All four Europeans studying this outbreak contracted the disease and almost every exposed native had been ill for some 4 days with fever and severe pains The manager of another farm where the disease was found in cattle had an attack which seemed to cure an old chronic malaria that affected him By this time 200 human cases were known none of whom had died so an adult native who was also a victim of chronic malaria was inoculated with blood containing the Rift Valley fever virus He developed a typical attack of the disease 3 days after inoculation but was not cured of his malaria Sheep inoculated with blood from this patient also developed typical Rift Valley fever One horse and two pigs were inoculated and failed to react The investigators believed transmission under natural conditions to be indirect and suggested that the mosquito *Tæniorhynchus brevipalpis* might be the vector They also believed that the disease probably had existed for years in Kenya Colony but had been confused with other diseases

Since the pioneer work of the above investigators many other animals have been found susceptible to inoculation with the virus of Rift Valley fever Among these are mice rats wood mice field voles dormice the golden hamster and the African buffalo Cats are relatively slightly susceptible the disease when it occurs in them being mild The gray squirrel can harbor the virus without being ill The rabbit guinea pig mongoose and hedgehog apparently are insusceptible as are birds reptiles and amphibians Certain Indian and South American monkeys were found susceptible though the disease is almost never fatal in them but African monkeys inoculated failed to develop the disease This appeared to be a natural rather than an acquired immunity as before inoculation no antibodies to the virus could be found in their blood whereas a few weeks after inoculation though no sign of illness developed antibodies were demonstrated

One attack of Rift Valley fever confers immunity against a second attack and immune bodies may be demonstrated in the blood serum as long as 4 or 5 years after infection Protective antibodies also may appear in the blood of persons repeatedly exposed to subinfective doses of the virus who never have shown clinical symptoms of the disease

Broom and Findlay demonstrated specific complement fixing antibodies in the blood in 1932 They were well developed in the serum 14 days after infection and persisted for at least 6 months They also were demonstrated in those repeatedly exposed to the disease who had not been ill with it but who presumably had had subclinical infections Livers of mice and rats with the disease were used as antigens fresh liver proving superior to dried

In 1933 Broom and Findlay using graded collodion membranes found the size of the virus bodies to be between 23 and 35 millimicrons and Mackenzie cultivated the virus 13 consecutive times without loss of titer or evidence of any change in its character in a medium of chick embryo and Tyrode s solution

In 1934 Kitchen found that exposure of the virus to methylene blue in the presence of light destroyed its infectivity for mice but did not destroy all its immunizing power The next year Mackenzie confirmed this work and also showed that a formolized antigen is equally effective as an immunizing agent The efficiency of these vaccines was in direct proportion to their concentration Immunity often was present 3 days after vaccination but 7 days as considered safer before assuming the animals to be immune The vaccine must be kept cool

Francis and Magill demonstrated in 1935 that Rift Valley fever can be transmitted by intranasal instillation in ferrets of pharyngeal washings

from human cases They believe the disease can be acquired naturally by man through the respiratory tract

In 1936 Mackenzie and Findlay produced a neurotropic strain of the virus by repeated intracerebral inoculation of mice This always produced encephalomyelitis without liver necrosis when injected intracerebrally In the same year Findlay gave an exhaustive discussion of the mechanism of immunity in Rift Valley fever to which the interested reader is referred Findlay and his associates have described a number of interesting phenomena such as the production of immunity without causing illness by the subcutaneous injection of a neurotropic strain of virus the unusual production of encephalitis by intraperitoneal injection of a pantropic strain etc using various animals for the purpose

Many investigators believe that there is a close relationship among the viruses of Rift Valley fever dengue yellow fever sandfly fever and the three day fever of cattle and discuss the possibility of interference phenomena or cross immunity among these diseases but no final conclusions have been reached

Pathology

In lambs the most striking lesion is extensive necrosis of the liver Smaller necrotic foci are found in the livers of adult sheep The spleen kidneys and lungs show nothing remarkable in lambs but in adult sheep tubular degeneration of the kidneys or nephrosis may develop The disease in lambs is too rapidly fatal for these to develop In the rare cases with bloody stools a hemorrhagic enteritis is found Extensive liver changes are absent as a rule in monkeys killed at the height of the disease For further pathological details including histological changes in animals the reader is referred to the reports of Findlay

Practically nothing is known of the pathology in man as the disease is so benign In the only fatal human case on record that reported by Schwentker and Rivers the patient had recovered from the virus infection per se and death resulted from pulmonary embolism secondary to thrombophlebitis and the pathological changes found were solely those of these complications or sequelæ Emulsions made of the patient s liver and mesenteric lymph nodes when injected into mice failed to produce the disease whereas during the active stage of his infection which he acquired while working with the virus in the Rockefeller Institute injection of his blood into mice produced the typical disease all the mice dying therefrom and showing the characteristic liver necrosis

Symptomatology in Man

The incubation period usually is from 3 to 6 days The disease begins with general malaise followed quickly by sharp rigors and headache The temperature may reach 103° or 104 F the eyes and face are flushed and swollen and photophobia may occur The tongue is coated and the breath foul Soon generalized pains develop and are most severe about the joints There may be a feeling of fulness or tenderness in the liver region nausea and vomiting may occur and exceptionally abdominal pain may occur but the liver and spleen can not be felt The fever usually lasts from 12 to 36 hours but the pains may persist for 3 or 4 days more One patient had a second period of fever with similar symptoms 3 days after the initial symptoms had cleared up and complained of headache and poor vision for some weeks The urine may show a mild febrile albuminuria bile pigments are absent from it and nothing of special import is found There may be a very brief moderate neutrophilic leukocytosis but this is soon followed by a moderate leukopenia with a relative increase in lymphocytes One patient showed a relative increase of monocytes Some myelocytes have been reported late in the disease The serum shows a normal content of bile pigments

Diagnosis

In man Rift Valley fever and *dengue* are similar in benignity duration and the presence of a filtrable virus as well as in many of their symptoms The latter disease is mosquito borne the former may be though this point is not settled The blood pictures are similar The important differential point is the absence of a rash in Rift Valley fever Dengue cannot be inoculated into sheep

Influenza usually shows marked irritation of the respiratory tract with severe tracheobronchial cough If this is absent the differentiation may be difficult Postinfluenzal prostration usually makes a more prolonged convalescence in severe cases Geographic location and occupation are to be considered and Rift Valley fever suspected in those exposed to infected flocks or in laboratory workers exposed to the virus

In the early stages of *yellow fever* before jaundice sets in the picture may be confusing but nausea with steadily increasing albuminuria should suggest that disease

Sandfly fever may simulate Rift Valley fever closely but the geographic distribution is different and the sandfly vector essential to the former disease

Trench fever is louse borne usually shows splenic enlargement and a rash and has a different geographic distribution

Certain brief *relapsing fevers* may be symptomatically confusing but the causative organisms are found in the blood in these diseases

Prognosis

In man this is good Most patients return to work within 2 or 3 weeks after the onset of the illness Kitchen reported 3 cases of accidental laboratory infection in which the patients returned to work in 20 16 and 14 days respectively Occasionally convalescence may be somewhat more prolonged The mortality in lambs may reach 90 per cent

Prophylaxis and Treatment

Vaccination with the vaccine of Kitchen and Mackenzie of susceptible domestic animals should be of great value It seems hardly necessary in man in whom the disease is so brief and benign

Treatment is symptomatic

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French fever is louse borne, usually shows splenic enlargement and a rash and has a different geographic distribution

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CHAPTER XIX

MUMPS

By CONRAD WESSELHOEFT

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Synonyms — Parotitis epidemica, cynanche parotidea (Latin); les oreillons (French); Ziegenpeter (German); fiebre urliana, paperas (Spanish); orecchioni, strangalioni (Italian).

Historical — In the Hippocratic writings[1] there is an account of an epidemic on the island of Thasos which leaves no doubt in the mind of the modern reader that the disease was mumps. There were swellings about the ears, often on both sides, which receded without suppuration.

and were accompanied sometimes by painful swelling in the testicles Although this epidemic disease was described somewhat vaguely down through the ages it remained for Hamilton[2] in 1790 to give us a classical description In 1893 appeared Comby s book[3] on the subject and in 1904 Schottmuller s monograph[4], both of which remain valuable sources of reference for their descriptions of varied clinical manifestations and epidemiology Contributions from military sources notably from the French Army have added greatly to our knowledge of this disease Indeed during the last war mumps became a serious problem among recruits in the United States Army in the matter of time lost in hospital[5] Within the past decade the discovery of the virus has initiated a new era in the history of this common malady

ETIOLOGY

In 1934 Johnson and Goodpasture[6] of Vanderbilt University Medical School isolated the virus of mumps In their first report these authors give an excellent historical review of many bacteriological investigations which began in 1881 and were followed by experiments with bacterially sterile filtrates of the saliva from mumps patients first instituted in 1908 Although successful transfers had been accomplished in animals the postulates of Koch were fulfilled first by Johnson and Goodpasture with the transfer of the disease to rhesus monkeys and after eleven transfers in monkeys successfully back to man then again back to a monkey

The fresh saliva from a case of mumps was injected into the parotid duct of a monkey Six days later a typical swelling of the gland took place The monkey was killed and a portion of the parotid gland was removed and placed in 50 per cent neutral glycerin then ground in a sterile mortar and taken up in 10 parts of 0 9 per cent sodium chloride solution This was placed in the ice box and the heavy material was allowed to settle The emulsion then was injected into the parotid duct of a second monkey After eleven such transfers each producing the typical parotitis the material was sprayed into the mouths of a group of supposedly non immune human beings and also into the mouths of a group known to have had mumps Among the thirteen supposedly susceptibles eight developed mumps within eighteen to thirty three days and four showed suspicious symptoms Those that had had mumps remained well

Aside from establishing the virus certain details of these experiments are of significance In the first place the material was found to be bacterially sterile and free from spirochetes It was filterable through a

Berkefeld filter and was resistant to glycerin freezing and drying Saliva taken on the first day of the disease from mumps patients proved to be most likely to be infective to monkeys that on the second day less so and that taken on the third day gave negative results The incubation period after direct inoculation into the parotid duct of a monkey was only six days while after spraying into the mouths of susceptible human beings the incubation period was eighteen to thirty three days Johnson and Goodpasture[6] point out that the experimental disease in man was milder than that usually seen in the epidemic form and that this may have been due to attenuation of the virus in the passage through the monkeys

Findlay and Clarke[7] have confirmed the first portion of the work of Johnson and Goodpasture Saliva used in their experiment was obtained forty-eight hours after the onset of mumps that obtained at the end of seventy two hours was not infective to monkeys

Pathology

The pathology of mumps parotitis in the monkey as depicted by Johnson and Goodpasture[6,8] consists of edematous swelling of the gland and its surrounding tissue with pin point hemorrhages in the capsule and destructive changes through the parenchyma including disintegration of the acinar cells and the presence of cytoplasmic inclusions There is an infiltration of mononuclear phagocytes and later of lymphocytes into the necrotic areas and about the ducts They attribute the edema to a diffuse vascular injury secondary to the fresh parenchymal lesions Healing takes place by removal of the debris and regeneration of acinal epithelium which restore the gland without scarring These findings coincide with Delater s pathological report on human mumps[9] The salivary gland material studied by this author came from a patient who died from sudden edema of the larynx that extended from an involvement of the submaxillary and sublingual glands while the parotid swelling was already receding A biopsy specimen of parotid removed on the third day of mumps was examined histologically by de Lavergne and his associates[10] From a review of the pathological reports to date (1939) and from their own findings they come to the conclusion that the lesions in the natural disease are in all probability the result of the virus entering the gland by some other route than by way of the duct

In such histological specimens as in those derived from the monkeys the polymorphonuclear neutrophilic leukocytes played no part in the inflammatory reaction However in a biopsy specimen obtained from a case

of human orchitis, operated on by G G Smith[11] the polymorphonuclear leukocytes were abundant The following report by Wolbach is incorporated in Smith s article

The process does not affect the testicle tissue uniformly There are groups of seminiferous (convoluted) tubules which are completely destroyed and distended with exudate separated by areas of normal and slightly affected tubules which contain large numbers of mitotic sexual cells though few mature spermatozoa

The exudate in the destroyed tubules consists chiefly of polymorphonuclear leucocytes and phagocytic endothelial leucocytes The cells of the tubules have mostly undergone a hyaline degeneration and are taken up by phagocytic endothelial leucocytes though there are occasional perfectly preserved mitotic sexual cells scattered among the tightly packed exudative cells

The intertubular connective tissue everywhere is edematous and between the tubules most affected contains coarse meshed fibrin small areas of hemorrhage and many polymorphonuclear and endothelial leucocytes

Among the groups of least affected tubules there are some with normal epithelium but with lumina partly filled with polymorphonuclear and endothelial leucocytes as if the process were spreading among the lumina

There are many more tubules however which show lesions involving a small portion of the circumference where it appears as if the process were extending from the intertubular connective tissue In these places numerous leucocytes are found in the act of migrating through the basement membrane of the tubules These small lesions contain deeply staining hyaline degenerated sexual cells hyaline fragments polymorphonuclear leucocytes and endothelial leucocytes The immediately adjacent epithelium is usually full of mitotic sexual cells showing the various stages of spermatogenesis

The tunica albuginea is edematous and there are small hemorrhages and zones of cellular exudate about blood vessels The cells about blood vessels are polymorphonuclear leucocytes and endothelial leucocytes

Mitotic endothelial cells in the lumina of capillaries occur in the tunica albuginea and intertubular connective tissue

Liquefaction necrosis is not present either in the tubules or in the connective structures

Manca[12] gives the autopsy findings in a fatal case of mumps orchitis, which occurred in a soldier He compares the pathology with that found in orchitis from other causes Further discussion of the pathology of mumps will be mentioned as we come to the various organs involved

PATHOGENESIS

Mumps is a natural disease of man only The experimental disease in monkeys is not communicable in the cages The virus shows a predilection for certain glands certain portions of the nervous system and occasionally other organs In its usual form mumps is an affliction of the salivary gland the parotids being by far the most commonly affected Yet many other glands of the body may become involved The gonads pancreas lacrimal glands breast glands thyroid thymus and Bartholin s glands are all susceptible in varying degree It is an established fact that the virus is excreted in the saliva It is then carried to the mucous membrane of a non immune individual From here it may go to the salivary glands and be distributed elsewhere through the blood stream On the other hand it may go from the mucous membrane directly into the blood stream and thereby reach the salivary glands or other organs. Philibert[11] has suggested that its portal of entry might be the conjunctiva from which it could pass along nerve channels to the encephalon and after an incubation period be spread through the blood stream to the parotid gland or other organs This new conception will be discussed under the heading Latent Encephalitis

Radin s[14] review of the epidemic of mumps at Camp Wheeler (1917–1918) shows that the parotid gland was involved in 4 243 cases the submaxillary in 440 and the sublinguals in 30 Catrin[15] on the other hand found the submaxillaries involved in one half of the cases This is more in line with my own experience Furthermore on careful examination the sublinguals may be found to be involved in at least one out of ten cases Non salivary manifestations of mumps are far more frequent than is generally believed In a careful study of 100 cases by Greene and Heeren[16] non salivary manifestations were found in 43

One can easily understand why this virus with a predilection for the salivary glands should also show a tendency to invade the pancreas because of the similarity of these structures However there exists a physiological relationship between the salivary glands and the sex organs which is worthy of mention This is seen in certain vertebrates Owen[17] states that during the breeding season a musky odor is emitted by the submaxillary glands of the crocodile and pervades their haunts The salivary glands of camels enlarge during the breeding season In the swiftlets of China the salivary glands become peculiarly active in the breeding season and secrete a substance akin to mucin with which they form their snow white nests the edible birds nests of the Chinese epicures[18]

Stephen Paget[19] in 1887 cited numerous instances in women where

this physiological relationship is shown by disturbed salivation with each menstruation as well as by enlargement of the parotid with each menstruation or with each successive pregnancy He discredited the idea that postoperative parotitis is always the result of oral sepsis pointing out that the parotid often becomes involved after injury to the genital organs a subject followed up by Morel[20] Taylor[21], Schottmuller[4] and Deaver[22] Non suppurative parotitis may also follow operations on the eye In Mikulicz s disease there is enlargement of the parotid and lacrimal glands often in association with a blood dyscrasia

This accumulated evidence shows on the one hand a physiological relationship between the sex organs and the salivary glands through the sympathetic stimulation of hormones and on the other hand the possible activation of a latent virus through injury to one organ whereby other susceptible organs may become invaded In mumps we are dealing with a virus which clinically at least is predominantly cytotropic The recent work of Goodpasture[3] on the predilection of certain viruses for certain tissues in the chick embryo comparable to the lesions of these viruses in man offers hope that new light will be thrown on the sphere of action of the mumps virus Moreover information is needed not only in regard to the interglandular relationship but also in regard to the relation between the glandular and the neurological manifestations

At this point in the discussion it is necessary to emphasize that the first manifestation of mumps is not always in the salivary glands Indeed an orchitis ovaritis pancreatitis or encephalitis may precede the involvement of the salivary glands although in the usual clinical course of the disease the reverse is the rule In fact in the general run of cases a parotitis and fever are the only symptoms noted Nevertheless evidence is accumulating which suggests that involvement of the encephalon is a rather frequent accompaniment of the parotitis if not actually a precursor This invasion of the encephalon may be so mild as to be recognizable only by examination of the spinal fluid A further discussion of this point will be found in the introduction to the Neurological Manifestations Suffice it to say that mumps is no longer looked upon as a local disease with possible complications but rather as a systemic disease displaying benign local symptoms in the salivary glands yet capable of arousing a wide variety of disorders through the predilection of the virus for many different and highly specialized tissues Thus the use of the term complication here is inaccurate since it can denote any secondary infection and these secondary infections such as otitis media bronchitis and appendicitis may occur during mumps as well as in any other contagious disease In rare instances a suppurative parotitis

may follow mumps and secondary virus infections of latent encephalitic origin may supervene also in the form of severe encephalitides

Best and Scott[4] showed that insulin like bodies were contained in the submaxillary glands The relation of the salivary glands to dextrose tolerance has been studied by Goldbladt[25] Quian[26] Zimmermann and Soskin[27] with conflicting results Thus the relationship between the internal secretions of the salivary glands and the carbohydrate metabolism requires further study

Dunlop[8] found the diastatic index increased in 60 cases of mumps studied by him All these showed well above 30 Wohlgemuth s units and some showed 200 units In 21 of these cases he used Loewi s method of installation of 1 1 000 adrenalin solution into the conjunctival sac with negative results from which he arrived at the conclusion that the diastase is derived from the parotids The feces were not examined His idea of basing the isolation period on the duration of the increased diastatic index is not tenable in view of the work of Johnson and Goodpasture and Findlay and Clarke referred to under Etiology

Carriers and Immunity

We are very ignorant on the question of carriers Assuming there are such we do not know in which organs the virus carries on its latent intracellular life although the virus presumably is excreted in the saliva Yet carriers there must be if we are to explain how the disease crops up year after year and with greater regularity in cities than in rural communities unless we assume that a persistence of the acute forms in the larger cities provides reservoirs of the virus

The majority of cases occur between the ages of five and fifteen the youngest case recorded in the literature being one day old and the oldest ninety nine years[9] However the disease is rare in infancy and old age Gordon[30] found that in Massachusetts 88 6 per cent of the reported cases were in children under fifteen years of age

Ringberg s[31] epidemiological study of mumps in Denmark from 1885 to 1894 presents the figures shown in Table I

The sexes are affected equally

In rural districts where the disease recurs at infrequent intervals many escape exposure Thus it is that military recruits and pupil nurses from farming communities being more susceptible through lack of exposure in childhood are so apt to develop mumps while in training Subminimal infections without symptoms may well afford a permanent immunity In this connection it is important to consider the volume of

TABLE I

Age groups	Cases
0–1 years	205
1–5	4 512
5–15	12 163
15–65	7 844
65–	50
	24 774

infection during an exposure in relation to the acquired resistance of the individual In such a disease as mumps without symptoms of coryza sneezing or cough the virus could be air borne only at close range with the nasopharynx or conjunctiva as possible portals of entry as well as contagious in the sense of direct contact from mouth to hand and hand to mouth Since mumps is confined to man man remains the reservoir and source of spread animals being infected by artificial methods only

One attack usually affords a lasting immunity but there are numerous instances on record of second or even multiple attacks[32] Four out of 100 cases reported by Greene and Heeren[16] were second attacks In 694 cases in the British Army reported by Macleod[33] 17 had had the disease before and one had had two previous attacks The following examples are from French military sources Léger[34] gives an account of a French soldier who was admitted to the hospital with mumps six times between November 1912 and March 1915 Each time mumps was epidemic in the units in which he served and on each occasion the diagnosis was confirmed by the characteristic course of the disease Albert[35] cites two buglers in one regiment each of whom suffered three attacks during one epidemic Fournié[36] reports that 5 of his 24 cases had had mumps before enlistment and Catrin[16] states that out of 157 cases 9 had had the disease one or more years before Manine[37] reports that out of 122 cases on board two ships in the French Navy 27 had had mumps previously These instances should be regarded as notable exceptions

This inability of certain individuals to establish a permanent immunity after an attack is another point which we are unable to explain Nevertheless the idea that a salivary gland establishes only a local immunity is entirely erroneous In the first place the involvement of a single salivary gland is followed by the same permanent immunity that occurs after multiple involvement Furthermore in recurrent attacks the same glands are apt to be involved the second time

Incubation Period

The average incubation period in the monkey after direct injection into the parotid duct was five days The exceptionally long incubation period in some of the human volunteers in Johnson and Goodpasture s experiment might be due to the attenuation of the virus through passage in several generations of monkeys In man the minimum period reported is eight days and the maximum thirty days The great majority of observations compiled from the literature show close to eighteen days and the average in all observations recorded is eighteen days[37] To my mind it seems probable that in the shorter periods cited the actual exposures preceded those of which the observers were aware Orr[38] tabulated the number of cases diagnosed daily in an epidemic of 902 cases in the Canadian Army The chart shows a very definite oscillation every eighteen days through six successive waves

Period of Infectivity

There is evidence[29] that the period of infectivity begins at least twenty four hours before the first symptoms are noted and for practical purposes one should put this date back another twenty four hours and begin isolation of non immune contacts in fourteen days after that and continue it for two weeks This procedure is feasible in military or institutional outbreaks with the first exposures Once an outbreak gets well under way the long and varied incubation period makes the at tempts at control often more costly than the unsatisfactory results warrant The fact that it has been impossible to infect monkeys with saliva taken from mumps patients seventy two hours after the onset suggests a short period of infectivity confined to the invasion On the other hand one must bear in mind that as one salivary gland subsides another may become involved thus prolonging the period of infectivity However it is exceedingly rare for one salivary gland to become involved after the swelling in the preceding gland has subsided entirely Consequently the duration of swelling in the salivary glands should be the maximum time of isolation unless other manifestations of the disease exist The virus is spread in the saliva in other words by everything the hand comes in contact with

We now know that the virus is resistant to drying but we do not know how long it is viable on the skin of the hand or in the presence of sunlight We have every reason to believe that ordinary soap and water

kills and removes the virus and that a room with its furniture and bed ding is disinfected by plenty of fresh air and sunlight in the course of about two to four hours The linen then may be washed in the usual manner The general principles of medical aseptic technique should be followed Now that the virus has been isolated we can hope for progress in the simplification of the control of this disease However our knowl edge of the nature of viruses and their communicability is still in its infancy Thus we are forced to take precautions based on generalities and it behooves us to utilize such knowledge of the nature and character of mumps as lies at our disposal

Involvement of the Salivary Glands

Symptomatology Diagnosis and Treatment —The usual manifestations of the disease give it the name of epidemic parotitis because the *parotid glands* are those involved most frequently and the only ones in the majority of cases In severe cases the swelling causes pain However, some tender ness is often present during the onset There is one particular point* of

* Eponyms in the literature on mumps are in need of correction Radin[14] has urged that a sign be accredited to Hathcock who first noted it in the U S Army epidemic at Camp Wheeler in 1918 This point of tenderness however was well described by Manine[37] a medical officer of the French Navy in 1913 Indeed it was well depicted as early as 1850 by Rilliet[40] of Geneva when he mentioned three points of pain on pressure about the angle of the jaw (superior) temporo maxillary articulation (posterior) level of mastoid tip (inferior) level of submaxillary gland Ascertaining these points of tenderness in the order of Rilliet is the equivalent of Hathcock s method The priority of the pain on pressure sign then belongs to Rilliet

The inflammatory area at the orifice of the parotid duct was studied carefully and reported on by Cowie[41] in 1920 Cowie claims no credit for the discovery Both Comby[3] and Catrin[15] had described the condition in 1893 and Schottmuller[4] also mentioned it in 1904 These earlier observations in no way detract from the valuable contribution made by Cowie As a matter of fact Cowie refers to this point of inflammation as the duct sign in mumps which is a very appropriate term This same condition is of equal diagnostic importance in connection with the duct orifices on the papillæ of the frenum.

The eponym given to the parotid duct is spelled in a variety of ways Maar[42] uses the term Steno through his biographical sketch and supplies the following information in a footnote The Danish form of this name is Niels Steensen while the Latinized form generally used by its owner was Nicholaus Stenonis The form usually adopted in our days is Steno which is due to the erroneous conception that Stenonis was really the genitive case of a name Steno Steensen was born in Copenhagen in 1638[43] The gist of all this is that this anatomist geologist philosopher and eventually Bishop of the Roman Catholic Church called himself in Latin Nicolas (the son) of Steen Since most of the modern spellings of this eponym seem to be wrong the term parotid duct has much in its favor

tenderness which frequently can be elicited namely at the angle of the jaw The tips of the first and second fingers are drawn with firm pressure down over the angle of the jaw the forefinger starting at the temporo maxillary articulation and the second finger passing behind and under the angle of the jaw This generally causes the patient to wince in the earliest stage of parotid involvement even before enlargement is apparent by inspection If the swelling occludes the duct there will be pain on taking a swallow of fruit juice vinegar or for that matter any food Without occlusion of the duct there will be no pain Using vinegar Miecamp[39] found this sign early in most of the soldiers that came under his care The opening of the duct frequently is red and sometimes teatulated It must be kept in mind that the orifice of this duct is often found to be teatulated in normal individuals In severe cases the swelling of the parotids may result in extraordinary disfigurement of the face Indeed the edema may spread up into the scalp and down into the neck *The overlying skin is stretched and may be exceedingly tender* to the slightest touch

One should palpate the *submaxillary glands* for tenderness and swelling Enlargement of the submaxillary glands gives rise to a double chin because of the accompanying edema This edema may extend even into the pharynx and the larynx Reverchon and his associates[43] have reported 6 such cases 3 of whom came under their observation One of these was saved by a tracheotomy *A case with fatal termination has been mentioned* already under Pathology The patient should be asked to raise the tip of the tongue to the palatal arch so that one may see the openings of the submaxillary ducts of Wharton on the papillæ of the frenum On close inspection the affected duct orifice will show a minute area of inflammation

Involvement of a *sublingual gland* is shown by its enlargement often with scattered petechiæ on the surface which may represent duct orifices In severe involvement of the sublinguals the tongue may become *markedly swollen*

The flow of *saliva* usually is normal but if at all affected it is oftener decreased than increased Numerous studies have been made of the chemistry and cellular contents of the saliva in mumps The saliva appears to be normal in reaction and consistency but it contains an increase in cellular elements

A fluctuating *fever* of varying degree usually is present but in the very mild cases the temperature may remain within normal limits The *blood* shows a moderate *lymphocytosis* but this is not constant[40, 46] In *the presence of very acute inflammation especially in the later stages*

of severe orchitis the blood picture is apt to swing to a neutrophilic leukocytosis

In the *differential diagnosis* one must consider first whether the patient has ever had mumps and secondly whether there has been a known exposure to the disease and if so when This circumstantial evidence is often of importance in making a very early diagnosis as it is with all communicable diseases A prolonged and intermittent swelling of a salivary gland leads one to suspect a calculus in the gland itself or in the duct Such a suspicion calls for digital examination and an x ray Sometimes swellings of the parotid follow surgical operations on the eye in elderly persons but also after abdominal operations and after operations on the genital tract[47] Some of these swellings are non suppurative but many go on to suppuration Oral sepsis in any typhoidal or septic state may lead to a parotid abscess An abscessed gland gives a fluctuant swelling with pus exuding from the duct and a neutrophilic leukocytosis A rare type of recurrent infectious parotitis with a purulent discharge from the parotid ducts and related to tonsillitis has been reported by Brown and Nevius[48] A tumor of the parotid usually is firm and appears gradually In some women the parotid glands enlarge with each menstruation and in others with each pregnancy[47] as has been mentioned under Pathogenesis Such physiological anomalies are, of course, rare Another rarity is Mikulicz s disease in which there is a persistent enlargement of the salivary and lacrimal glands with or without a lymphatic leukemia and deficient salivary flow

The *treatment* of salivary mumps is purely symptomatic Mouth washes are quite unnecessary The intake of fluids takes care of the oral cavity The gastrointestinal canal needs no interference unless constipation occurs Routine catharsis was denounced by Hamilton in 1790 and his logic in this respect is substantiated by our modern knowledge of the disease The application of an ice bag or a hot water bottle is at times comforting Reliance on other measures puts me in mind of the sympathetic magic of red flannel so favored by our ancestors The use of convalescent serum will be taken up under prophylaxis

INVOLVEMENT OF THE GENITAL ORGANS

Orchitis

Orchitis rarely occurs before the age of puberty Steiner[49] reports a case of orchitis in a nursing infant nine months old This occurred during an epidemic in which father mother and infant contracted the

disease both the father and the infant having an accompanying orchitis Fabre[64] reports an orchitis in a boy of nine and Armand[31] an orchitis followed by atrophy in a boy of eleven *In this connection it is interesting to note that mumps orchitis has occurred in the undescended testicle* in this position the gland is apt to remain undeveloped or undergo partial atrophy In the case described by Ross[4] the patient was fourteen The affected testicle was on the right retained in the inguinal canal and caused such continued pain that it was removed by operation *It was found* to show all the signs of acute inflammation on microscopical examination Another case[36] of this kind was in a negro aged thirty three *Here* the left testicle was involved in the inguinal canal There was splinting of the left rectus muscle with intense pain and delirium

At and beyond the age of puberty I[47] have found the average incidence of orchitis in 8 153 collected cases to be 18 per cent The incidence varies greatly not only in different epidemics but in the same epidemic Thus Dukes[34] *found a variation from 3 3 per cent to 37 5 per cent in* different epidemics of mumps at Rugby School At an army post in France in April 1915 de Massary and Tockmann[58] found orchitis in 27 per cent and in May of the same year in only 5 per cent with practically the same number of cases of mumps in each of these months At the Military School at Halifax[36] among 20 cases of mumps there were 10 cases of orchitis and on board H M S Ardent[37] there were 12 cases of mumps all of which developed orchitis These figures are cited to show the influence of the *genius epidemicus* and the difficulties encountered in any attempt to evaluate modern measures aimed at prevention

Orchitis usually occurs within ten days after the onset of salivary gland involvement but it may occur simultaneously or may precede the parotitis I have collected 30 cases[47] in which the orchitis was primary and 64 cases in which orchitis was the only manifestation The diagnosis in these cases was based on strong circumstantial evidence and on the course of the disease In mild cases the testicle has returned to normal in a week or ten days

The *treatment* of mild and moderate cases consists in supporting the *scrotum on a wide strip of adhesive plaster across the thighs* A T bandage is then applied loosely to give lateral support if the patient lies on his side An ice bag or hot water bottle sometimes is of comfort but occasionally the patient prefers to dispense with all these measures which in my experience in no way affect the outcome Diathermy has *been reported to be of benefit*[55] *The use of serum in connection with* orchitis will be considered under Convalescent Mumps Serum in Treatment and Prevention

During the embryological descent of the testicle two layers of peritoneum are carried down into the scrotum The outer layer is the tunica vaginalis which forms the inner surface of the scrotum The inner layer, the tunica albuginea forms the dense glistening fibrous cover to the testicle When the mumps virus invades the testicle the inflammatory reaction takes place which has been fully described under Pathology A mild reaction produces only moderate discomfort and subsides spontaneously without permanent damage However if the reaction is more violent the swelling produces marked tension of the fibrous cover with severe pain and threatens a pressure necrosis within the gland We are not dealing here with that simple toxic process which takes place in the parotid where the acinar cells are readily replaced but with an actual choking process and threatened destruction of entire areas of glandular tissue which if continued leads to irreparable damage and subsequent atrophy

In severe orchitis the testicle enlarges to three or four times its normal size Its enlargement is magnified by the edema of the overlying scrotum and the formation of hydrocele fluid The scrotum may become almost a centimeter in depth and of a bluish red color There is apt to be a chill and high fever sometimes associated with delirium The patient may lie motionless and repel any attempt at examination or may writhe about in an agony uninfluenced by one half grain (30 mgm) of morphine to say nothing of support from an adhesive strip across the thighs or the application of an ice bag or a hot water bottle

The *treatment of severe orchitis* is surgical and to be effective must be carried out before pressure necrosis takes place It is impossible to set a time limit The condition may be relatively mild for two or three days and then suddenly flare up into violent activity or it may be violent from the very onset If the condition becomes severe surgical interference is indicated One is guided largely by the pain fever incompressibility of the testicle and the amount of swelling The operation consists in making an incision through the edematous scrotum toward the outer wall of the testicle As the incision penetrates the tunica vaginalis the hydrocele fluid spurts out Through a three centimeter opening the tunica albuginea is brought into view and this may be studded with small petechiæ It is firm from internal pressure A cross incision is made with the scalpel just through the fibrous layer so as to release the tension in two directions care being taken to avoid any visible blood vessel The testicular tissue bulges out into the shallow incision Owing to the pressure little or no bleeding takes place There will be bleeding if the tension is not great or if the incision is made in a mild orchitis or in one that is already subsiding One stitch may be taken in the scro

turn if the outer wound gapes Sterile pads then are held in place by a T bandage This operation is simple and affords immediate relief I have seen a fever of 103 F drop to 100° F within four hours The result is comparable to the evacuation of pus from an abscessed cavity *This drop in the fever will not occur if other manifestations of mumps are co existent* The operation is contraindicated in mild cases and after the tension under the tunica albuginea is subsiding There is no need of delivering the testicle through the scrotum as has been recommended[59] Owing to the swollen condition of the scrotum at the time of operation *the ultimate scar may be only one centimeter long and may be* found with difficulty after six months In one case on our wards operated on within thirty hours of the onset the wound was healed in one week at which time the testicle which had been swollen to four times its original size had returned to normal size In another case operated *on later the testicle did not return to normal size until the fourth week* and after six months a slight atrophy had taken place

Much is written about the necessity of keeping mumps patients strictly confined to bed to avoid orchitis Such statements are at variance with the carefully checked clinical results supplied by Dukes[54] at *Rugby School in England and by Radin[14] at Camp Wheeler Both* of these authors found that strict bed rest did not diminish the incidence of orchitis Another notion which has been advanced particularly in the military literature is that trauma to the testicle during the incubation period induces orchitis Weigert[60] has recommended dismounted drill for *cavalry when mumps is epidemic I have compiled the incidence of* orchitis reported in the various branches of military service and from civilian sources the summary of which is as follows[47]

INCIDENCE OF ORCHITIS

	Cases of Mumps	*Cases of Orchitis*	*Orchitis per cent*
Infantry	1 1[illegible]	49	1[illegible]
Cavalry	162	[illegible]	22
Miscellaneous Army & Navy	6 5[illegible]	1 119	[illegible]
Civilian	309	64	20 7
	8 153	1 468	18 0

From this table it does not appear that trauma from the saddle is of any significance The idea that the virus is carried by the hand to the urethra and from here to the testicle is another fallacy A careful clinical experiment carried out by Radin[14] at Camp Wheeler showed this idea to be entirely erroneous Rolleston[61] quotes French and German observers

who found a lower incidence of mumps orchitis among soldiers in the front lines than at the base, ascribed by these writers to the difference in sexual activities

Atrophy of the testicle of varying degree follows practically all severe cases of orchitis In 347 cases of orchitis compiled from the literature[67] atrophy resulted in 190 or 54 7 per cent There is doubt whether this atrophy is ever complete but unquestionably it is often sufficient to impair the testicular function Fortunately the unaffected testicle usually undergoes a compensatory hypertrophy and serves the function of procreation Only 16 per cent of the cases of orchitis are bilateral and in these atrophy usually occurs only on one side Benard[6] investigated 175 000 cases of mumps reported in the French Army and was unable to establish one single case of sterility among them Even with double atrophy he was unable to find azoospermia However an instance of sterile marriage is recorded by Giovanni[63] in which the seminal discharge showed no spermatozoa as the result of bilateral orchioepididymitis followed by bilateral testicular atrophy and induration of the epididymes. As pointed out by Stengel[64] sterility implies the lack of sufficient sex cells while impotence refers to the inability to complete the sexual act The fear of being sterile is a result of testicular atrophy after mumps may result in a serious mental complex which promotes impotency Reassurance that there will be no sterility given early in the development of orchitis is an important part of therapy

Since orchitis from mumps rarely occurs before the age of puberty and even if bilateral rarely if ever completely destroys all glandular tissue the disease has never produced a true eunuch[47] Sexual defects may be brought about as occurred in a case depicted by Morris[65] but even in this case which suffered a bilateral atrophy at thirteen there was some healthy glandular tissue remaining to respond to a testicular tissue implant at the age of twenty seven Unfortunately Morris was unable to follow the subsequent history of the case (from a personal communication from Dr Morris to the author)

Epididymitis

Epididymitis may be associated with orchitis or may exist alone It is much less painful than in the gonorrhoeal variety In general there is discomfort rather than pain Hydrocele fluid forms in varying amounts Operative interference is not indicated The swelling and the tenderness persist for five to ten days and subside spontaneously The fever is relatively lower than in orchitis

Prostatitis

Prostatitis was reported in 5 per cent of the adult male cases of mumps studied by Greene and Heeren[18] It is usually of a mild degree Robinson[66] reported atrophy of the pro tate presumably of mumps origin

Oophoritis

Oophoritis appears to a much less frequent extent than orchitis Greene and Heeren[18] observed this condition in 5 per cent of adult females It is attended by low abdominal pain sometimes radiating to the umbilical region and sometimes into the lumbar region with tenderness in the lower abdominal quadrant on the affected side On vaginal examination the diseased ovary may be found to be enlarged and very tender If ovaritis is severe and especially if it is bilateral there may be acute pain repeated chills each followed by high fever and sometimes accompanied by menstrual flow out of time

Dalkas[67] cites 28 cases in which the menstrual function was not disturbed thus portraying the usual benign nature of this condition He then describes a case under his own care in a woman of twenty-eight of regular menstrual habits A bilateral parotitis occurred twelve days after the last period A bilateral ovaritis followed ten days later with fever vomiting and pain starting in the epigastrium The ovaries were tender and three times their normal size A menstrual flow took place lasting three days She was well in seven days Menstruation was re established a few days later and after that was regular for three months She then underwent a normal pregnancy and thereafter menstruation was again regular

The menstrual disturbances of mumps have been discussed recently by Beclere and Demange[68] Their case was thirty two years old had had four children and had always had regular normal and painless periods The onset of the parotitis coincided with the menstrual period which was on time and lasted for the usual three days Three days after the end of the period double ovaritis took place with hemorrhagic uterine flow lasting three weeks stopping three days before the beginning of the next period The next three periods were profuse after which she became pregnant

McNaughton[69] reports the case of a girl of eighteen who had always had painful but regular menstruation Ten days after a double epidemic parotitis she developed severe pain in both ovarian regions and menstruated out of time After a delay of six weeks regular menstruation

was resumed, but thereafter it was painless Ohlmacher [6] reported a primary right sided ovaritis which he discovered on operation for a suspected appendicitis The ovary was edematous and the surface presented a few minute petechiae Three days later the patient developed a typical bilateral mumps parotitis

Josephson [1] describes a case of double ovaritis in a woman of thirty eight The onset was eleven days after a double parotitis and coincided with menstruation which was on time Owing to the persistent low abdominal pain she was sent to the hospital where an enlarged right ovary was found Five months later a laparotomy was performed The left adnexa were normal but the right ovary was fist size and on section was found to be sclerosed and cystic The interest in this case lies in the fact that the patient had enjoyed good health until the attack of mumps ovaritis which led later to the removal of a diseased ovary Josephson discusses the possible part played by the mumps and reviews the literature

Among the cases of possible mumps ovaritis collected by Berger[7] there are several which occurred before puberty One of these was in a girl of six who showed a bloody discharge from the vagina

The *treatment* of ovaritis is symptomatic Acetylsalicylic acid in conjunction with codein controls the pain in the mild cases and morphine in the more severe ones An ice bag or a hot water bottle may afford some comfort but needless to say cannot be expected to influence the pathological process

Moore [3] reports a stillbirth at seven months following a severe bilateral parotitis in which decompensation occurred from an old mitral stenosis

The *vulvovaginal glands* may become swollen *Mastitis* is another rarity This may occur in both sexes[3] and may be either unilateral or bilateral Gould[74] reports a unilateral mastitis accompanying the parotitis Mastitis is characterized by a benign course of short duration

PANCREATITIS

Pancreatitis was observed by Greene and Heeren[16] in 7 of their 100 cases of mumps in young adults I had occasion to examine 16 cases of mumps in the infirmary of a boys school and in 3 of these there was definite tenderness over the pancreas It has been stated that the condition is rare among children but more frequent in adults[75] This assertion is not substantiated by reports in the literature Edgecombe[76] reports 5 cases between the ages of nine and eleven and Freund[77] records 8 cases in children from three to eight years old in one epidemic Neu

rath [5] reports 7 cases among three girls and four boys two at seven two at ten and one each at nine twelve and thirteen An interesting point in the *genius epidemicus* of mumps is that among these cases two families supplied two cases each The author reviews the subject and cites from the literature only one case that of Sharp[79] in which glycosuria was reported Farnam[80] collected 119 cases reported in the literature with one fatality most of these being derived from military sources Janbon[81] and his associates report 2 cases among 83 cases of mumps in a French Army Hospital Sylvest[8] has reviewed the subject more recently

Involvement of the pancreas may precede accompany or follow the *swelling of the salivary glands*[77] *but more often it occurs as these are subsiding* I have seen one case in which an exploratory laparotomy was performed and in which the pancreas was found to be swollen and firm I based the diagnosis of mumps pancreatitis on the circumstantial evidence of previous exposure sixteen days before and the benign course No other positive manifestations of mumps occurred

Pancreatitis is manifested first by definite tenderness over the region of this gland This objective sign may be the *only symptom* in mild cases but such tenderness in itself does not establish conclusively the existence of pancreatitis *Nevertheless in more severe cases the gland may be actually palpated*[76, 77] Pain in the region of the pancreas of a constant or intermittent character vomiting constipation or diarrhœa and fever may occur but the condition usually lasts only a few days The treatment consists in adjusting the diet to the symptoms

A lowered sugar tolerance curve on the fifth and sixth days in three severe cases of mumps was observed by Mommsen and Mayer[83] However White[84] has shown *that carbohydrate tolerance can be disturbed* during the course of many other infections besides mumps Hirsch Kauffmann[85] was unable to find a variation in sugar tolerance in 2 cases of mumps in diabetics In 4 severe cases of mumps without evidence of diabetes I found the daily fasting blood sugar to be normal However in 6 diabetics with mumps I found a rise in the fasting blood sugar on the sixth day in two cases This experience has led me to feel that blood sugar changes in mumps are not of much significance

Cuche[86] in 1897 and Harris[87] in 1899 introduced the idea that *damage to the pancreas in the course of mumps might lead to diabetes mellitus* The latter reported a man of forty two who showed symptoms of diabetes one month after an attack of mumps Patrick[88] collected 5 cases of acute diabetes following an attack of mumps Couronne[89] enlarged on this collection with a total of 8 To this he adds a sudden fatal coma on the second day of an attack of mumps in a diabetic girl of eleven Mommsen

and Mayer[83] have drawn on material from the literature to support their contention that damage to the pancreas in the course of mumps may be an underestimated cause of diabetes Gundersen[90] has come to the same conclusion after reviewing the subject He supplies a chart which shows that previous to the use of insulin the deaths from diabetes in Norway in the ages from ten to twenty, present a curve with peaks which follow closely four epidemics of mumps However, the investigations of White[84] in Joslin s clinic do not indicate that a past or recent history of mumps has a significant bearing on the etiology of diabetes mellitus

Involvement of Other Organs

In a study of 700 cases of mumps in soldiers Capitan[91] frequently found enlargement of the *spleen* Greene and Heeren[16] observed splenomegaly 19 times in 100 cases In the autopsy reported by Manca[12] the spleen was twice the normal size weighing 300 grams the capsule was thin smooth and tense and the cut surface presented a dark red markedly protruding pulp The *liver* was enlarged also and weighed 1,100 grams the cut surface was cloudy and reddish brown The *kidneys* were moderately enlarged The capsule stripped easily The cortex was somewhat broad cloudy and yellowish gray the medullary substance was dark red (The histological findings in these organs are not given) Nephritis has been reported occasionally Radin[14] does not report this condition among his 5 756 cases at Camp Wheeler In 800 cases I have never seen more than a slight transient albuminuria Schottmuller[4] discusses the nephritis of mumps at some length He also cites a few cases of *thyroiditis* culled from the literature In the case described by Dalto and Pos e[9] an ovaritis followed the parotitis and this in turn was followed by an uneventful thyroiditis of five days duration Sailer[93] found 6 cases of transient enlargement of the *thymus* on palpation just above the manubrium with the patient s head thrown back There was no tenderness and no stridulous breath but there was some dyspnoea The diagnosis was confirmed by x ray evidence This condition was observed in the epidemic reported on by Radin

The *respiratory system* is interfered with only through the pread of edema from the submaxillary glands and to a slight extent when the thymus becomes involved The circulatory system also is rarely affected *Myocarditis* has been reported[61] In 3 fatal cases of encephalitis of the psychotic type myocarditis was said to be the cause of death and in at least one this condition was confirmed by autopsy[94 95] Bradycardia has been noted by various authors[76 7 96] in connection with pancreatitis

Such slowing of the heart rate corresponds to the sympathetic phenomena observed in acute affections of the pancreas Bradycardia has been studied also by Benard[61] and Margarot[96] in connection with the oculo cardiac reflex Although these authors express divergent views as to the significance of vagotonia there can be no doubt that it is at times well marked in mumps One should not confuse such slowing of the pulse rate with the bradycardia sometimes caused by increased spinal fluid pressure in the presence of encephalitis

Neurological Manifestations

The virus of mumps may attack various portions of the nervous system The most common result is an encephalitis This may be so mild as to be recognizable only by the spinal fluid findings or it may be of varying degrees of severity with obvious symptoms and signs of meningeal irritation It is this meningeal element which accounts for the common use of the term meningo-encephalitis However this prefix is not generally applied to other encephalitides and there appears to be no justification for its selection for the encephalitis of mumps

Latent Encephalitis

Latent is the term used to designate the mildest form of encephalitis which is recognizable only by an increased number of cells in the spinal fluid there being no symptoms whatever to suggest meningeal irritation A pleocytosis may occur in the course of other infectious diseases as pointed out by Herrick and his associates[97] but in no other infectious disease are so many cells found in the spinal fluid without symptoms of meningeal irritation Monod[98] in 1902 was the first to report this condition about the eighth day in 6 out of 8 cases of mumps In 1917 de Massary Tockmann and Luce[99] found a pleocytosis in all of the 40 cases of mumps they examined whether or not meningeal symptoms were present A pleocytosis however was not always found in the fluid drawn at the first puncture Silwer[100] found a pleocytosis ranging from 11 to 259 cells in 10 out of 50 cases of mumps showing no meningeal symptoms Finkelstein[101] found a pleocytosis in 16 out of 40 cases at the Willard Parker Hospital Four of the 16 showed well marked symptoms of meningeal irritation Six showed mild symptoms and in the remaining 6 there were no clinical signs or symptoms which would even suggest the possibility of meningo-encephalitis In the 6 cases without meningeal symptoms the cell count ranged from 15 to 880 cells I have re

ported the finding of 400 cells in an adult male with parotid mumps where there were no clinical signs or symptoms to suggest the presence of an encephalitis.[3] Much work needs to be done on this subject before we can have any proper idea of the actual frequency of latent encephalitis in this disease, but it does appear to exist often enough to indicate that the mumps virus is capable of producing an encephalitis of the mildest form, in direct contrast to rabies and the eastern strain of equine encephalitis.

Philibert[13] has elaborated a hypothesis based on the assumption that this latent encephalitis is a constant accompaniment of mumps. He suggests that the virus may enter the body through the conjunctiva and from there reach the encephalon. According to this hypothesis the virus establishes an encephalitis and is then eliminated through the salivary glands which being susceptible become inflamed. This idea of a constant primary latent encephalitis explains very nicely why one may have the first manifestations of mumps in the testicle, the ovary, the pancreas or the nervous system before involvement of the salivary glands. Indeed if this were the case we could understand how these organs could be invaded in any possible sequence and how we might have any one of them show the only outward manifestation of mumps. Philibert compares the pathogenesis of rabies to support his theory. The rabies virus, he says, can enter the body by way of the conjunctiva without producing any conjunctival lesion. When the central nervous system is involved this rabies virus is secreted in the saliva without injury to the salivary glands because the rabies virus is not cytotropic. He also mentions the fact that the rabies virus can be recovered in the dog from both the testicle and the pancreas in neither of which it produces any injury. He goes on to explain that mumps differs from rabies in that the virus of the former manifests a cytotropic action particularly on the parotid glands. The fault in this hypothesis is the fact that at the present time evidence is lacking that a latent encephalitis exists in all cases of mumps and in the second place that the virus is constantly present in the spinal fluid.

Montgomery[10] has called attention to the fact that in the majority of instances the encephalitis follows the parotitis. However, the more susceptible salivary glands might well show signs of injury earlier than would usually be taken to develop clinical encephalitis. It will be recalled that Johnson and Goodpasture[6] were able to infect healthy susceptible human volunteers by spraying the virus into the mouth. This result does not preclude the possibility that the virus may reach the conjunctiva by subsequent transfer from the mouth to the eye by the hand of the volunteer. Recent animal experimentation by de Lavergne

and his associates[103, 104] brings support to Philibert's thesis These investigators found that after the fifteenth day of incubation in man the spinal fluid becomes characteristically neurotropic for rabbits on injection into the cerebral fluid producing a lymphocytic meningitis and encephalitis Spinal fluid obtained during the parotitis of man produced this same result in the rabbit while that of the controls gave negative results *The virus however was not recovered from the rabbits after encephalitis* was established Thus we do not know as yet whether the mumps virus itself was responsible for the lesions or whether a rabbit encephalitis virus was activated by this procedure Further studies along this line are necessary before one can accept Philibert's hypothesis

Another question of importance is whether the pleocytosis and the clinical meningeal symptoms are fundamentally of encephalitic origin From our knowledge of other viruses we are led to surmise that the encephalitis of mumps originates in a primary attack on the encephalon and that the disturbance of the meninges and choroid plexus is secondary Such pathological reports as we have indicate that acute encephalitis exists primarily and that the disturbances of the meninges and choroid plexus are secondary It is well to consider here that in the preparalytic stage of poliomyelitis with its primary central pathology the initial symptoms and signs of meningeal irritation are identical with those of mumps encephalitis The close similarity of the meningeal manifestations of these two diseases makes it highly probable that these manifestations in mumps are secondary to a centrally located lesion in the encephalon

Clinical Encephalitis

The *incidence* of encephalitis in the course of mumps derived from the presence of clinical signs is difficult to determine For instance there is no means of determining the incidence in childhood at which age the majority of cases of mumps occur The disease itself is reportable but this particular manifestation is not Military observations since they are made in hospitals are often more trustworthy than those derived from home treatment Furthermore much depends on the accuracy of the observer Dopter[105] a leading French authority on all forms of meningitis gives us the most reliable criteria He found clinical signs of encephalitis in 158 of the 1 705 cases of mumps that came under his observation or 9 8 per cent Dalto[75] *reported 21 among 250 cases or 8 per cent and* Steinberg[106] an incidence of 10 per cent in 210 cases while Greene and Heeren[16] reported 11 among 100 cases

Dalto remarks on the relative frequency of signs of meningeal irrita

tion in the presence of orchitis an observation in accord with my own experience This explains the view expressed by Holtz[107] that encephalitis is more common in adults than in children and also why more cases are reported among males than among females At the Kingston Avenue Hospital Brooklyn from 1934 to 1939 there were 29 cases of mumps encephalitis the majority of these falling in the age group of five to ten years Curiously enough only 5 of the patients were females Two cases occurred in brothers five and seven years old Tabor and Newman[108] the authors of this report, cite from the literature 2 other instances of this condition in siblings one of which was in identical twins

I am of the opinion that clinical encephalitis is a more common accompaniment of mumps in childhood than is generally recognized The citation by L H Smith[109] of 15 cases among 2 500 reported cases of mumps in Portland Oregon in 1935 and the 9 cases cited by Birnberg[110] in eighteen months in Minnesota (1935) do not portray the true incidence Had these two observers had the opportunity to examine all the reported cases of mumps it is highly probable that many more cases showing signs of encephalitis would have been found in these localities The former pertinently remarks that since physicians are becoming more polio myelitis minded more cases are recognized than hitherto

At this point it is of interest that Roux[111] reported only 3 cases of encephalitis out of 274 cases of mumps in the French Army in 1914 that in the United States Army from 1918 to 1919 Radin[14] reported only one in 5 756 cases at Camp Wheeler Brooks[112] none in 1 059 cases at Camp Upton Haden[113] 9 out of 475 at Camp Lee and Larkin[114] 2 out of 2 400 at Camp Taylor a total of 15 in 9 964 cases Undoubtedly many mild symptoms of encephalitis were missed by the Army medical officers just as they are missed in general practice but it is also apparent that severe cases must have been about as rare as they are in the community at large where almost nine tenths of the cases of mumps occur in childhood

In this connection it is of interest to note that mumps encephalitis is being recognized more frequently than formerly Silwer[100] states that in the Naval Hospital at Karlskrone in Sweden in 1931 when not so much attention was given to the possible occurrence of meningeal symptoms in mumps such symptoms were observed in 1 per cent of the cases and in 1932 and 1934 in 9 per cent and in 1935 in 8 per cent' At the Haynes Memorial Hospital from 1914 to 1933 there were only 3 cases of mumps encephalitis recorded in 824 cases of mumps while from 1933 to August 1 1940 mumps encephalitis was observed in 18 out of 226 cases and several of these had been referred to the hospital because of the encephalitis

When the encephalitis is the first manifestation of mumps it is designated as *primary* While this sequence of events is unusual there are numerous reports of such cases in the literature[94b, 113, 114, 116] Just as it is possible to have orchitis as the only manifestation of mumps so encephalitis may be the only manifestation Howard[117] has reported 3 such cases in a mumps epidemic among soldiers The circumstantial evidence of exposure coupled with an appropriate incubation period and the course followed may permit a speculative differential diagnosis from preparalytic poliomyelitis

Clinical Picture of Encephalitis

The clinical picture of mumps encephalitis is even more varied than that of acute poliomyelitis Nevertheless in its most common form it is indistinguishable in its symptoms signs and spinal fluid findings from preparalytic poliomyelitis except by the circumstance of the association with other undoubted manifestations of mumps These encephalitic symptoms may precede accompany or follow the involvement of the salivary glands but in the majority of instances encephalitis occurs as the parotitis is subsiding or within ten days of the disappearance of the swelling

A typical picture of the mild form is taken from my teaching clinic[118]

This boy of eight came down with a mild attack of mumps nine days ago The parotid swelling subsided and all went well until the sixth day of convalescence when with no history of injury he became feverish complained of headache and vomited in the afternoon and again during the night The family physician noticed an increasing rigidity of the neck and spine and for this reason the patient was hurried to this hospital

On admission three days ago the child was very drowsy with occasional short periods of restlessness There was no difficulty in swallowing and he took liquids well The eyes were closed or half closed when drowsy and staring when restless The pupils were equal and reacted to light There was no evidence of any paralysis of the eye muscles and no nystagmus No swelling of the parotid sublingual or submaxillary glands could be detected The openings of the parotid and submaxillary ducts were not remarkable The face was flushed Temperature was 104.6 F pulse 132 respiration 34 There was a well marked rigidity of the neck and spine When one attempted to raise the head with the child lying on his back the entire body was lifted and this was accompanied by pain In the sitting position it was impossible for the child to put his head between his knees or to touch his chin to his knees The *spine was stiff without opisthotonus and the entire* back was tender No tremors were seen There was a slight Brudzinski and a moderate bilateral Kernig sign The knee jerks were diminished and equal ankle clo

nus and Babinski absent as well as the Gordon and Oppenheim signs The abdominal and cremasteric reflexes were present the testicles being normal A very pronounced tache cerebrale was present The ears were entirely negative There was no nasal discharge and the throat showed only a slight injection of the fauces A few very small glands could be felt in the neck Nothing abnormal could be elicited in the heart and lungs and the abdomen was negative on palpation

A white count showed 9 000 leukocytes with 25 per cent polymorphonuclear and 75 per cent lymphocytes Lumbar puncture showed a slightly hazy fluid of the ground glass variety under a normal pressure of 6 mm Hg Twenty c c of spinal fluid were drained off and immediately examined The cell count was 1 4 0 chiefly lymphocytes Sugar and globulin both were present A culture of the spinal fluid was reported as showing no growth The urine was negative

In short here was an obviously sick boy one week after the onset of mumps, with symptoms indistinguishable in every way from a preparalytic poliomyelitis but with the circumstantial evidence of his mumps convalescence Here he is today three days after admission with no rigidity of the neck or spine and a normal temperature

In this case we have merely the symptoms and signs of meningeal irritation but in another boy of four in my clinic the typical encephalitic picture unfolded Here there had been a convulsion at home and on admission the bilateral parotitis was said to be subsiding There were convulsive twitchings of both arms and both legs and spastic extension of the fingers Marked rigidity of the neck and spine were present The patient was extremely restless and thrashed about in his crib in contrast to the drowsiness of the first case This restlessness persisted in spite of ½ grain (30 mgm) of phenobarbitol fifteen grains (1 gm) of bromides and 1/24 grain (2 5 mgm) of morphine At lumbar puncture clear spinal fluid spurted out under increased pressure The cell count was 570 with 63 per cent lymphocytes and 27 per cent polymorphonuclear neutrophiles At the second lumbar puncture on the second day the flow of fluid was not increased and the cell count was 426 He became quiet and on the third day the temperature dropped from 102° F to 99° F, and thereafter he was bright and quite normal in every way Convulsions are rare in mumps encephalitis Comatose and hemiplegic forms have been described[119 1 0]

A recent case[1 1] is reported from Paris in a man of forty two in association with a unilateral orchitis where the temperature reached 40 4 C (104 9° F) on the fourth day of a bilateral parotitis with submaxillary involvement There were photophobia vertigo severe headache and vomiting rigidity of the neck positive Kernig sign and myoclonia Marked mental depression was present with spasmodic weeping The patient was entirely well in twenty days

Psychotic forms are extremely rare An extraordinary case reported recently by Urechia[94b] was of the primary type The onset of the mental symptoms preceded the bilateral parotitis by six days The patient was a woman of fifty four who had had eleven children and who had always enjoyed good health On the first day of her illness she awoke with a sense of anxiety and fear of death On admission to the hospital she presented a confused mania got out of bed often made disordered movements of the hands grimaced used obscene words and when asked questions repeated them and expressed ideas of persecution Eventually she refused nourishment was tube fed and expired on the eighth day The autopsy findings of the brain are given in detail The cause of death was attributed to myocarditis which unfortunately is merely mentioned as having been found

Personality changes have been reported[108] *but this is certainly a very* rare sequel to mumps encephalitis As these authors Tabor and Newman remark the subject needs further follow up studies In Ley's case[110] the condition persisted for only six months in contrast to those permanent sequelae observed after other encephalitides

Another type met with is *encephalomyelitis* In the case described by Lemierre and his associates[122] the condition appeared five days after the onset of a bilateral parotitis with nystagmus tremors coma and bilateral facial paralysis The spinal fluid was under increased pressure and contained 200 cells Recovery was complete in two months Another case is that reported by Fortney[123] of a *transverse myelitis* which followed twelve days after the onset of a bilateral parotitis and a mild bilateral orchitis There was no headache pain in the neck or back The trouble began as a tingling in the soles of both feet followed by a feeling of numbness There was loss of control of the bladder and rectum with urinary retention and overflow without pain There was no response to laxatives *The onset began with weakness in the legs One* lumbar puncture was done which showed the spinal fluid under normal pressure with 5 cells There was slight rigidity of the neck The bladder paralysis continued for six months Complete recovery followed in seven months The author cites two other cases from the literature one of which was well after eight weeks and the other showed no improvement after nineteen months

Another case of transverse myelitis is described by McKaig and Woltman[124] under the heading of parotitic myelitis This occurred in a girl of sixteen following two weeks after mumps The onset showed malaise tired feeling pain between the shoulder blades and weakness in the legs This was followed shortly after by paralysis of the urinary

bladder and the anal sphincter Anesthesia for all forms of sensation developed below the second costal interspace The spinal fluid was under normal pressure and contained 3 lymphocytes and 1 neutrophile At a subsequent lumbar puncture there were 7 lymphocytes and 2 neutrophiles No improvement had taken place seven months later Another case similar in nature with a fatal outcome is reviewed by these authors Here the onset was ten days after the epidemic parotitis Dénéchau[1..] describes a case of myelitis developing twenty five days after mumps

These cases of encephalomyelitis merge so strongly into the picture of encephalopathies not of mumps origin that the activation of other latent encephalitides through the mumps virus is suggested In the light of our present knowledge it is impossible to say that the mumps virus per se is capable of producing these clinical pictures just as it is equally impossible to say that the opposite is true I am led to this consideration by an experience in three fatal cases of whooping cough who died of encephalomyelitis and came to autopsy at the Haynes Memorial Hospital[1 6] The clinical evidence indicated that they succumbed to an encephalitis in the course of pertussis but the histological evidence pointed to a violent encephalomyelitis such as our pathologist had never before seen in autopsy material in pertussis The virus of eastern strain equine encephalomyelitis was recovered from the brain tissue of two of these cases and all three came from an area in which this disease was epidemic in horses and in human beings

This digression serves to point out that an encephalomyelitis may develop in the course of an infectious disease and be entirely foreign in its pathology to that of the original infection Consequently in mumps it is conceivable that cases of encephalomyelitis may originate from some latent encephalitic virus stimulated into activity by the virus of mumps Until virus studies are made on the various encephalopathies which occur in association with mumps it will be impossible to differentiate mumps encephalitis from other encephalitides arising in the course of mumps

This leads us to certain *epidemiological considerations* Gundersen[1 7] draws attention to the epidemiological relationship between epidemic encephalitis and mumps Both he says are essentially winter diseases and have the same topographical distribution This is borne out by the incidence of mumps by month in the United States Army during the last war[109 128] Gundersen points out that the epidemiological peculiarities of epidemic encephalitis suggest that this disease is only a special manifestation of a widely spread infection and that mumps might be the instigator of cases of lethargic encephalitis Epidemics of mumps recur regularly in Norway every eight or ten years At these times one may

find clinically mumps encephalitis or an epidemic encephalitis associated with the epidemic parotitis Birnberg[110] observed 9 cases of mumps encephalitis in Minnesota in the course of eighteen months The increase in the incidence of epidemic encephalitis during this same period led him to suggest a causal relationship between these two diseases He drew attention to the increased number of cases of encephalitis following measles vaccination and other infectious diseases with the advent of epidemic encephalitis In 4 cases reported by Gordon[109] the symptoms and pathology strongly suggest an epidemic encephalitis superimposed on mumps

Pathology of Encephalitis

The few pathological reports at our disposal give little help in solving this problem for no virus studies have been made as yet in these cases and therefore we do not know whether the mumps virus or some encephalitis virus was responsible for the lesions One is forced to depend solely on the clinical association of mumps with the lesions found and such evidence is unreliable *Melkurg and Woltman*[104] *give an excellent review of the* pathological findings In the case of a patient who died in six hours reported by Dopter[105] edema was the outstanding process Unfortunately microscopic sections were not made De Lavergne and his associates[103] present a review of another group of autopsy findings with special emphasis on the case of Wegelin where an encephalitis developed eleven days after the parotid and submaxillary involvement with death three days *later There were lymphocytic infiltration of the meninges blood* vessels with disseminated small hemorrhages and islands of demyelinization Such islands were reported also in Bien s case of an eight year old child who developed convulsions eight days after the parotitis and died in twenty four hours cited by de Lavergne and his associates and by Melkurg and Woltman Urechia[94] gives a still later review in which he cites the cases of Wegelin and Bien as being worthy of consideration In both there were islands of *myelin degeneration He then cites the case of Cathala* and his associates where a bulbar death took place on the ninth day and no myelin degeneration was found at autopsy He then describes the findings already mentioned in his own cases of a psychotic type Here again no evidence of myelin degeneration was present He reports however that the inflammatory process in the meninges and encephalon had almost all cleared up death resulting from myocarditis Thus we have *two diametrically opposed findings as regards the important point of* demyelinization

The results of experiments in monkeys, cats and rabbits by direct inoculation are not convincing for there is nothing to prove either that the virus of mumps was present in the inoculated material or that this material did not activate a latent virus. Conflicting assertions have been built up on these premises regarding the nature of mumps encephalitis, but to my mind any exact pathological interpretation must await corroborative virus studies.

With all this in mind and from a strictly clinical point of view, I have drawn up quite arbitrarily the following considerations for making a *differential diagnosis*. The circumstantial evidence of active or very recent mumps or even exposure to mumps, and meningeal symptoms of short duration often with high spinal fluid counts are important criteria on which to base the diagnosis of mumps encephalitis. On the other hand a prolonged drowsiness, nystagmus, ocular muscle paralyses, incoordination of the skeletal muscles, tremors, jerking and twitching, flaccid and spastic paralyses and persistent relatively low spinal fluid cell counts suggest that some other encephalitis virus is at work.

The Spinal Fluid of Encephalitis

Previous statements regarding the cell count in the cerebrospinal fluid need further discussion. It is customary to draw up a differential diagnosis based on these findings but this is hazardous because of the complexity of the pathology. In the latent form one may have a cell count of 800 with lymphocytes predominating or just enough cells to constitute an abnormality without increase in the fluid pressure. At the onset of clinical encephalitis one may have a definite increase in pressure with only one or two cells. A few days later the pressure may be normal while the count may be markedly increased. On the other hand the cell count at the start may be high up in the hundreds with the fluid presenting a ground glass appearance yet under normal pressure. This same thing holds true in acute anterior poliomyelitis. Indeed Herrick and Dannenberg[130] have shown that in the course of many infectious diseases with and without signs of meningeal irritation a relatively mild pleocytosis may be present. However this does not approach the high counts seen in mumps, poliomyelitis, lymphocytic choriomeningitis and equine encephalomyelitis. Influenzal, tuberculous and the purulent form of meningitis should be kept in mind as possibilities in differential diagnosis.

The highest count I have observed in mumps encephalitis was 2,106 with 68 per cent lymphocytes. This case presented marked meningeal symptoms. However the cell count in mumps as in poliomyelitis, ap-

pears to bear no constant relationship to the severity of the meningeal symptoms. This is explained on the ground that a sudden swelling of the encephalon or a disturbance of the hydraulic stabilizing function in the choroid plexus will put the spinal fluid under pressure and give rise to meningeal symptoms before any cellular outpouring takes place, whereas if the swelling is slight or has subsided the pressure may not be increased and yet many cells may be present. The cellular response is primarily a lymphocytosis, but if a serofibrinous meningitis takes place the number of polymorphonuclear neutrophiles will be increased. Further examination of the spinal fluid reveals nothing of positive diagnostic importance. The albumin, globulin and sugar may be somewhat increased and the chlorides slightly decreased. The colloidal gold curve is either normal or conforms to a meningitic reaction.

Treatment of Encephalitis

The specific treatment of encephalitis consists in releasing any increased spinal fluid pressure by lumbar drainage. The headache sometimes is so much relieved by this procedure under skilled hands that the patient asks to have it repeated when the pain again becomes severe. In mild cases where there is no doubt of the diagnosis a lumbar puncture is not necessary. In encephalomyelitis the urinary bladder should be watched for distention. The patient should be kept in bed for several days after the temperature has reached normal and all symptoms have disappeared. The duration of this rest depends of course on the length and severity of the encephalopathy.

NEURITIS

Various types of polyneuritis have been mentioned by authors. Several[10, 14, 131] have suggested that this may originate from a meningoradiculitis, that is, from damage to the nerve trunk near its root. This is supported by the scant pathological evidence at hand where severe serofibrinous meningitis has been found. This could involve the cranial and spinal nerve roots. However, there is no way of knowing whether the mumps virus does this alone or in association with some other encephalitic virus.

Facial nerve paralysis does occur with mumps. This is of a temporary nature. It is the general belief that the virus extends directly from the parotid to the peripheral part of the nerve. In this connection one must keep in mind the fact that toxic products are evolved by the activity of

the virus This is exemplified by the pyrexia of orchitis which often subsides as promptly after incision of the tunica albuginea as after the evacuation of pus from an abscess cavity In these facial nerve palsies the virus itself may not penetrate into the facial nerve, but the toxic products may do so Courand and Petges[13] report 7 cases of temporary facial nerve paralysis in one epidemic McKaig and Woltman[14] cite 3 cases of bilateral facial paralysis It is interesting that neither Frid berg[131] nor Bassoe[131] mentions mumps as a cause of the auriculo temporal syndrome a vasomotor disturbance induced by suppurative parotitis

Trigeminal nerve paralysis has been recorded also as well as a variety of cranial nerve palsies involving the eye muscles and the palate Rolleston[61] has raised the question whether some of these instances may not be due to missed cases of diphtheria One case cited by Butler and Wilson[13] suggests a possible connection with mumps A temporary *ocular paralysis* followed three weeks after an attack of this disease Their second case occurred one month after mumps and was permanent In this case the mumps etiology is not convincingly established Temporary disturbances of accommodation have occurred[4, 136]

Optic Nerve — Temporary and permanent damage to the optic nerve has been reported[4] Young[137] reports a bilateral optic neuritis with complete blindness coming on thirteen days after mumps in a ten year old boy associated with encephalitis and terminating in a complete recovery of normal vision two months later Swab[138] found optic atrophy taking place five weeks after a mumps encephalitis Unilateral blindness from glaucoma and staphyloma following mumps is recorded by Woodward[139] Mikulowski[140] describes a bilateral *panophthalmitis* followed by atrophy of the eyeball In the cases cited by Young and Swab we can visualize a meningo radiculitis while in the 2 other cases the destruction of the eyeball suggests a secondary infection followed by nerve atrophy

Deafness and Meniere s Disease — Deafness appears in three different ways In the first type the first sign of deafness is an inability to hear with one ear as in using the telephone[141] In the second type deafness in one or both ears comes on abruptly with pain In the third type the deafness is ushered in by the acute symptoms of Ménière s disease with or without severe pain[142, 143, 144] In the 51 cases assembled by Boot[14] vertigo was present in 29 absent in 7 and not recorded in 15 Nausea and vomiting were recorded in 26 and unconsciousness in 5 Tinnitus with rushing or tingling of bells may precede or accompany the first signs of auditory impairment The drum is normal on inspection Deafness of a partial or complete and usually permanent character follows Fortunately the deafness is more often unilateral than bilateral

Hubbard[145] has estimated that 3 to 5 per cent of the 50 000 deaf mutes in the United States in 1915 owed their condition to mumps Considering the size of the population and the number of cases each year in this country the incidence of complete deafness on the basis of this computation must be very small indeed We have no means of knowing the number of cases of partially impaired hearing Presumably it is a very rare sequel Among 44 cases where the age was recorded only 5 occurred below the age of eleven[14]

The occurrence of deafness appears to have no relation to the severity of the salivary gland involvement Wallerstein[146] and Bristow[147] state that a unilateral deafness may occur on the opposite side from a unilateral parotitis This is confirmed by the protocol of 51 cases compiled from the literature by Boot[14] Furthermore there seems to be no direct relationship between the onset of deafness and clinical symptoms of encephalitis[141] Consequently the deafness appears to be independent of the severity and of the proximity of the parotitis and although at times associated with clinical encephalitis seems to be by no means dependent on this condition The permanence of the deafness of mumps is in marked contrast to the temporary deafness seen in typhoid fever where a toxic neuritis is conceded Moreover when neuritis of the facial nerve takes place in mumps the injury is of a temporary character

Aside from the possibility that a meningo radiculitis may result from a severe encephalitis the subject of deafness from mumps should be considered under the heading of *labyrinthitis* rather than of nerve deafness In the first place there is the frequent association with disturbances of the static labyrinth in moderate or severe forms In the second place the permanent character of the damage differs from the temporary injury to the facial nerve Finally Mauthner[142] found islands of deafness in the milder cases These islands remind us of the localized atrophic changes observed in the testicle Such islands of deafness could result from degeneration of groups of filaments in the cochlear branch of the auditory nerve but atrophy of the cochlear branch of the eighth nerve or any filaments of it would follow any permanent damage within the cochlea and there are no generally accepted means of determining whether the nerve or the cochlea is at fault The static labyrinth and the cochlea can be involved simultaneously or independently as in the case of the epididymis and testicle Whether the virus is active in the semicircular canals and the cochlea giving rise to vascular damage resulting in cell necrosis in these sense organs is a matter for speculation based on our knowledge of the action of the virus elsewhere in the body for the actual pathology is unknown If an actual labyrinthitis of this nature does take

place then the atrophy of either the vestibular or the cochlear branch of the eighth nerve would be secondary to the destruction of the sense organ Though the vertigo tends to disappear through compensation, the hearing continues to remain impaired It would thus appear that the deafness from mumps may well be of labyrinthine origin rather than of a strictly neuritic origin Since the entire labyrinth, including the cochlea and the static labyrinth consists of an embryonic outgrowth of the nervous system such injury would be of neurotropic origin

General Considerations as to the Treatment of Mumps

The treatment of mumps resolves itself into the use of logical measures in the handling of the various manifestations of the disease Such measures have been considered under the different conditions taken up in this treatise Obviously a patient with fever is better off in bed but beyond this one cannot go because as I have shown strict bed rest for one week does not lower the incidence of orchitis nor is there any reliable evidence that such a regimen lowers the incidence of involvement of other organs It is well to keep in mind the fact that an important feature of the pathology is edema That the swelling can be checked by the application of an ice bag is contrary to my experience In the event of pain cold or heat may be of comfort In the vast majority of cases the salivary glands need no local application whatever Constipation of course needs correction but routine catharsis has no logical place in our modern conception of this virus disease

The following historical note on the treatment of mumps in 1810 gives food for thought lest we fancy that our modern ideas and methods are beyond criticism in the future

I endeavored to bring on suppuration by frequently renewed hot poultices Blisters and spirituous applications brought the disease to a speedier termination while the application of flannel or leaving it to nature only protracted it for a day or two longer and when the inflammation had once proceeded to the testicle, no method was successful in bringing it back to the parotid gland After the metastases to the testis had taken place I was on my guard against its proceeding onward to the brain A strict antiphlogistic regimen was enjoined full and repeated purging employed and where the habit of body pain and febrile symptoms pointed out the necessity or repetition of venesection it was had recourse to Emetics were given in several cases with the evident effect of shortening the period of inflammation and when at its acme of rapidly reducing the swelling Headache developed in two cases In

these "no time was now lost in taking active measures They had formerly been bled and purged the bleeding was repeated to the extent of 24 ounces from a large orifice drastic purgatives were given the whole head was shaved blisters applied to the temples and cold over the rest of the surface In this way the headache was relieved in 36 hours"[47]

At times I have been under the impression that my own recommendations for surgical intervention in severe orchitis and for lumbar drainage have been regarded as unnecessarily drastic Perhaps the poor sailors on H M S Ardent were as grateful to their ship surgeon as my patients have been for their recovery After all fatalities are rare in this disease under all forms of treatment The hydraulic principle of releasing pressure mechanically can be carried to illogical extremes No advantage can be gained by drainage when no evidence of increased pressure exists either in the testicle or in the spinal canal The idea that routine repeated lumbar drainage in all cases of encephalitis would decrease the incidence of deafness is an example of poorly conceived therapeutic efforts Nevertheless it is conceivable that the release of increased spinal fluid pressure by drainage might be of benefit not only to the encephalon but also to any inflammation about the exits of the cranial nerves

Convalescent Mumps Serum in Treatment and Prevention

Convalescent mumps serum has been advocated to combat the acute stage As pointed out by Rivers[148] once a virus has attached itself to a cell or passed within a cell antibodies supplied by therapeutic serum encounter great difficulty in reaching the cell in effective doses However Gradwohl and his associates[149] employed 5 c c doses with benefit according to their opinion Metzulescu[150] used convalescent serum in 3 cases with encephalitis in which he abstained from lumbar punctures and in 5 cases with orchitis in which 20 to 25 c c were given daily by the intramuscular route during the pyrexia The results were so highly satisfactory that he strongly recommended its use for control of the acute symptoms

The question arises whether a supply of antibodies in the form of convalescent serum at the onset of the parotitis could prevent the virus from reaching other organs through the blood stream De Lavergne and Florentin[151] concluded from their investigation that when 20 c c of this serum is given with the onset of the parotitis the incidence of orchitis is reduced Of their 113 patients so treated only 4 developed orchitis and only 2 showed signs of encephalitis On the other hand of 17 patients

given the serum of serum treated mumps cases orchitis occurred in 7 cases and encephalitis in 3 while in the 107 controls orchitis appeared in 24 per cent and encephalitis in 9 per cent Iversen[1] reports on 703 cases of mumps among soldiers Of those given the serum 20 per cent had orchitis while in the untreated cases the incidence was 30 per cent Hinckley[14] used an average of 18 c c in 23 cases with results which were distinctly favorable as compared to the controls Thalhimer[154] asserts that large doses 40–60 c c will alleviate complications such as orchitis and oophoritis

However equally good results have been reported by Italian and French authors from the use of horse serum in the form of diphtheria antitoxin This non specific serum therapy was much in vogue at one time both for the treatment and prevention of orchitis Bonnamour and Bardin[155] review the incidence of orchitis in the French Army They cite a variation from 10 per cent to 25 per cent in different epidemics and present their experience with 65 soldiers with mumps in 1918 All were given diphtheria antitoxin Five showed orchitis on admission to the hospital and in these the condition appeared to be arrested by this treatment Of the remaining 60 only 3 developed orchitis or 5 per cent Mallie[156] adds these 60 to others collected from the literature to give the sum of 128 treated in this manner with development of only 9 cases of orchitis He then cites other cases of orchitis relieved by the prompt administration of this serum A recital of these results from non specific serum therapy is given here merely as a control for the results previously mentioned from convalescent serum

An experience of my own in a mumps series of 100 males above the age of puberty is enlightening These cases were given a preparation of lead favorably reported on by Martiny[157] The first 82 did not develop testicular involvement constituting the largest series on record without orchitis But in the following 18 there were 5 cases of orchitis and one of epididymitis after which this treatment was abandoned as futile The conclusion reached from this experiment was that the *genius epidemicus* of mumps was sadly in need of further research as a basis for therapeutic investigations With this observation in mind I can not ascribe so much value to convalescent serum treatment as has been ascribed to it in the literature If we reason from analogy with other virus diseases it seems probable that only very large doses could influence the course of the disease after the incubation period is passed Indeed there is no satisfactory proof that even this is possible Thus the application of this method of treatment must remain largely of theoretical interest

The early use of *convalescent serum* after exposure *to prevent mumps*

is an entirely different matter The early work of Hess[158] has been confirmed repeatedly He used 6 to 8 c c of whole convalescent blood injected directly into the muscle without any anticoagulant with 100 per cent success in exposed small children Zeligs[159] obtained 100 per cent protection of non immune contacts boys from ten to eighteen years of age with 5 c c of convalescent serum seven days after exposure Barenberg and Ostroff[160] reported an incidence of 15 per cent in treated cases as against 39 per cent in the controls in an epidemic already under way Thalhimer[154] reports 96 to 100 per cent protection and Kutscher[161] 98 per cent protection in sizable groups The latter gave the serum four days after exposure Gunn s[15] observations are enlightening because individuals who were injected soon after exposure did not contract the disease at the end of the incubation period but subsequently did from later exposures to the controls Further evidence as to the prophylactic value of convalescent serum is unnecessary We can prevent mumps with convalescent serum but there is no assurance that this prevention is of lasting character On the contrary an individual would have to be given serum with every subsequent known exposure throughout life if we would attempt to guarantee him protection

Mumps is a prevalent epidemic disease of relatively mild character in the general run of cases It does the least damage especially in the male between the ages of five and ten This does not mean that serious manifestations do not arise in this age period Preventive measures can be effectively put in use during the incipiency of epidemics in schools military establishments and other institutions We must not lose sight of the fact that convalescent serum affords only temporary protection The futility of the precautionary measures adopted by municipal boards of health is seen in the fact that approximately nine tenths of the urban population has had mumps at the age of sixteen Familiarity with this disease engenders a respect for the advantages both to the individual and to the nation of an active immunity acquired through having mumps in the grammar school period

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HISTORICAL NOTE

Fillatow is credited by Kracke[1] as first describing in 1885 an infectious illness with generalized lymph node enlargement Pfeiffer in 1889 described an epi demic disease in children characterized by glandular enlargement and a similar epidemic was described in the United States by West[3] in 1896 However sporadic cases with similar manifestations were not commonly recognized as cases of glandular fever occasional reports of cases under the term monocytic angina suggest this entity but it was not until reports had appeared of several small series of cases [5] beginning in 1920 that general interest was aroused Sprunt and Evans descriptive term infectious mononucleosis has become generally accepted in this country The accurate description of the characteristic blood morphology by Downey[7] in 1923 afforded a precise standard for diagnosis The increased interest and reports of cases thereafter were augmented in 1932 by the fortuitous observation of Paul and Bunnell[8] that sheep cell agglutinins frequently were pres ent in high titer only in this disease and in serum sickness This test as well as the blood morphology tended to establish the identity of sporadic cases with the epidemic ones originally described as glandular fever The voluminous litera ture was reviewed comprehensively by Bernstein[9] in 1940 with report of addi tional cases

INCIDENCE AND EPIDEMIOLOGY

The earlier conception that the disease was not common must now be revised in view of the frequency of reported cases The incidence of the disease is un known because in medical practice patients with presumably minor respiratory and other infections are not hospitalized commonly and blood counts and mor phology are not studied unless the duration of illness is prolonged or the diagnosis obscure The fact that in colleges and institutions such cases are hospitalized more commonly and differential blood counts are studied more frequently ac counts for the frequency of the finding of this disease in such groups[1] in addition to the fact that the disease occurs usually in young adults Physicians who are conscious of this entity observe it not uncommonly in young adults in private practice It would appear that this is a widely distributed entity and that its recognition is proportional to the physician s interest and is limited by the infre quency of laboratory study under certain conditions of practice The epidemics reported have been chiefly in schools or institutions where close environmental living conditions suggest particular opportunity for contact infection The epi demics observed by the writer in young adults have been in fraternity houses or

CHAPTER XIX-A

INFECTIOUS MONONUCLEOSIS

By C. A. McKINLAY AND HAL DOWNEY

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PART II HEMATOLOGICAL AND PATHOLOGICAL ASPECTS

PART I

CLINICAL ASPECTS

By C. A. McKINLAY

Definition — Infectious mononucleosis is characterized by throat infection, lymphadenopathy and lymphocytosis with quite typical blood morphology and

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dormitories and suggest that the disease becomes epidemic in adults only occasionally and under conditions of close contact In the sporadic cases observed in the hospital although strict isolation has not been attempted, but few, if any, contact cases have been recognized Low grade communicability would appear to be present in adults

Sex and Age Incidence

Males appear to be more susceptible in reported series[9 11] in the ratio of 3 to 2 In 124 personally reported cases [1 12] 94 were males This represented a distinctly higher proportion of males than existed in the student body Common experience indicates that while individuals of all ages may be infected the highest incidence is in children and young adults Epidemics have occurred more commonly in children and sporadic cases are reported more frequently in young adults

Seasonal Incidence

Cases observed over a 22 year period appear to be distributed fairly evenly by seasons although the total yearly variation over an 8 year period was from 4 to 18 cases

ETIOLOGY

The etiology is not known Murray and co workers[14] in 1926 isolated *Bacterium monocytogenes* apparently belonging to the listerella group, from rabbits having a generalized infection associated with an increase in the number of large lymphocytes Nyfeldt[15] in 1929 reported the isolation from the blood of a patient of an organism which he called *Bacterium monocytogenes hominis* with which he produced the cellular blood picture in rabbits Other observers failed to isolate the listerella organism in infectious mononucleosis and still others grew the organisms in cases of meningoencephalitis Olson[16] obtained only negative results from the injection of emulsions of lymph nodes into monkeys and guinea pigs Wising[7] produced in macacus monkeys, after injection of lymph nodes from patients with infectious mononucleosis mild clinical symptoms of generalized lymphadenitis and a slight increase in the mononuclear cells of the blood No organisms were cultured from the lymph nodes of both man and monkey Van den Berghe[18] and co workers succeeded in reproducing the disease in successive passages from monkey to monkey through inoculations with patients' blood passed through a Seitz filter Zolman and Silverman[19] report meningoencephalitis in a patient with infectious mononucleosis and consider possible virus etiology with acquired neurotropic properties

Clinical Picture

Incubation Period

This is not known but report[9, 1] of incubation periods of 11 days in cases after a single exposure would suggest that interval as most nearly correct

Presenting Symptoms and Signs

At the onset it should be stated that personal observation is in keeping with that elsewhere noted by Isaacs that there are cases of unknown frequency with minimal systemic and local manifestations whose identity is established only by the chance finding of disturbance of blood morphology Nevertheless the clinical picture presented by sporadic cases usually is well defined and may be described best by emphasis of certain outstanding groups of symptoms in relation to their frequency

Throat and Upper Respiratory Tract

In the 124 cases personally reported[7, 1, 8] and observed with other staff members at the Students Health Service at the University of Minnesota over a period of 22 years an upper respiratory infection was the presenting symptom in 72 per cent of cases and was manifested by sore throat in 47 per cent of those with recorded findings

While the onset of sore throat may be similar to that caused by tonsillitis or pharyngitis of other origin it tends to be less abrupt the temperature reaction is not so great and the course is longer When a case presents itself with sore throat of several days duration the prolongation of which is not due to a suppurative complication of tonsillitis such as quinsy this entity is strongly suggested and may be established by change of blood morphology in cases where the adenopathy is not distinctive There may be injection of the fauces tonsils and pharynx 48 per cent or follicular tonsillitis or pharyngitis may occur 35 per cent The exudate not infrequently tends to form confluent areas over the tonsils and pharynx The throat structures often are injected moderately instead of deeply but the associated edema may be very marked and the associated dysphagia interfere with adequate fluid intake

Occasionally there is marked nasal congestion and paranasal sinusitis and laryngo tracheo bronchitis with varying emphasis of localization may supervene While this latter type of respiratory infection is not distinctive the associated adenopathy may suggest this entity

Lymphadenopathy

Generalized lymph node enlargement is the physical manifestation encountered most frequently. The type of this adenopathy is so characteristic that it alone may suggest the condition. Cervical lymph node enlargement occurred in 91 per cent of 65 cases and axillary enlargement in 81.5 per cent. The lymph nodes, particularly in the posterior cervical triangle, participate in the process, extending deep under the sternomastoid muscle at about its middle and somewhat inferior to the angle of the mandible where, sometimes asymmetrically, they form a confluent mass, although the individual nodes elsewhere in the chains are discrete.

The nodes, as a rule, are not markedly tender, are somewhat elastic on palpation and often are free from swelling of the adjacent tissue. In adults parotitis has not been simulated, and the submaxillary and other nodes of the anterior cervical triangle do not enlarge characteristically and in this contrast with the adenopathy associated with tonsillitis. The axillary nodes present the same characteristics and often are enlarged. The epitrochlear nodes may participate also. Inguinal adenopathy in males is interpreted less readily but appears to be demonstrable not infrequently as a part of the process. Occasionally, enlargement of the cervical lymph nodes has been the presenting complaint, sometimes without associated respiratory infection.

In well established cases adenopathy may rarely not occur at any time, and in one recent instance the nature and persistence of the tonsillitis suggested this entity before lymphocytosis appeared and without the occurrence of lymph node enlargement at any time.

Systemic Febrile Type

Cases with febrile onset with headache, aching sensations and malaise without localizing signs are the most difficult to recognize early in the course and may continue to be obscure until tonsillitis or pharyngitis, lymphadenopathy and lymphocytosis occur, or until high titer of sheep cell agglutinins appears in the blood. The latest stages of the disease are illustrated best by one case in which there was retardation of lymphocytosis and pharyngitis until 14 and 19 days respectively after onset. A persistent diphasic temperature associated with recurrent chills may suggest this entity. Although the patient may be quite ill the degree of prostration usually does not approach that noted in sepsis. In cases with only systemic reaction bizarre behavior of the leucocytes may be the first suggestive sign with early leucopenia followed by leucocytosis due to absolute lymphocytosis.

Abdominal Symptoms

Initial symptoms sometimes are referred to the gastrointestinal tract with nausea and vomiting infrequently with abdominal pain In personally observed cases in adults appendicitis has not been simulated in children it is reported [3] to have caused confusion The spleen becomes palpable in about one half of the cases by the end of the first week The degree of enlargement usually is mod erate but rare examples of marked hypertrophy are known The liver edge is not commonly palpable In one epidemic it was palpable in 90 per cent [3] in an other in 100 per cent of the cases Jaundice is uncommon but may appear according to de Vries [4] as the initial symptom or along with the glandular enlarge ment or as the only symptom The jaundice has been assumed to be the regurgi tant type associated with enlargement of lymph nodes in the portal fissure How ever acute hepatitis has been suggested sometimes and Kilham and Steigman report that liver biopsy in one patient with deep icterus showed parenchymatous changes with well marked focal acute hepatitis

Central Nervous System

Headache as a predominating symptom not infrequently occurs and in the type without respiratory localization may direct attention toward central nervous system involvement including meningitis or encephalitis Certain cases through out their course complain of severe headache Drowsiness is also an occa ional symptom Cerebral complications in 13 reported cases have been reviewed by Thelander and Shaw[45] The common symptom was headache which with other nervous manifestations may appear as much as two weeks before the character istic lymphadenopathy and splenic enlargement and which may be mistaken as evidence of lymphocytic choriomeningitis or of acute encephalitis As a rule the nervous signs and symptoms disappeared without residuum It is of interest to note that Thomsen and Vintrup reported 6 deaths in 500 cases collected in Denmark In 4 fatal cases symptoms of respiratory failure prevailed and autopsy vealed severe degeneration of cells in the respiratory center

Skin

A rash develops occasionally In observed cases a fine maculopapular rash developed 6 6 per cent Templeton and Sutherland [8] in a report on the rash of infectious mononucleosis conclude that it is usually a fine maculopapular type indistinguishable from German measles Tidy [7] has described a typhoid like rash closely resembling rose spots appearing between the 4th and 7th days Scarlatini

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cases these agglutinins may be absent Davidsohn has reviewed the status of the sheep cell agglutination and absorption tests in infectious mononucleosis

False positive Wassermann reactions have been reported with enough regularity to suggest unusual frequency in this disease and always have been found to be transient although noted as long as 3 months In personally observed cases a positive reaction has occurred rarely

The spinal fluid occasionally shows pleocytosis irrespective of the occurrence of abnormal neurological signs In a few cases personally observed the cell counts were normal although there were signs of meningeal irritation

Urinalysis has shown nothing more than transient albuminuria encountered frequently in febrile illness Anemia never has been pronounced In one instance a crisis in familial hemolytic jaundice was precipitated

Course of Disease

The patient when first examined usually has been ill two or more days The temperature tends to increase through the first week reaching a maximum of 101° to 103 F in about one half of the cases and above 103 F in 18 per cent of 50 cases of illness The temperature often is diphasic with two or more peaks during twenty four hour periods After a daily increase the maximum temperature tends to subside followed sometimes by one or two wave like recrudescences before it becomes normal after total duration varying up to 26 days Cases are described with moderate temperature extending over a few months The average duration of illness of 45 cases was 14 4 days and average hospitalization time 10 0 days All cases with prolonged course have had some type of respiratory infection and usually exudative tonsillitis and pharyngitis have been present and of marked degree Marked prostration although infrequent may occur Recurrences are uncommon

Differential Diagnosis

This disease entity must be differentiated first from tonsillitis pharyngitis and laryngo tracheo bronchitis associated with organisms commonly demonstrated such as hemolytic and sometimes viridans streptococci Diphtheritic type of membrane has been simulated at times except that the exudate usually has appeared bilaterally in the follicles sometimes later becoming confluent Vincent s angina does not present the same extent or localization of the lesion or the systemic reaction

The systemic cases without respiratory localization are the most difficult to recognize and in these the possibility of other infections including sepsis may be

form and urticarial eruptions also are described Purpuric areas have been noted rarely in the skin and mucous membranes and purpura hemorrhagica has been simulated

Laboratory Findings

Accurate determination of the change of *blood morphology* remains the most trustworthy criteria for diagnosis The behavior of the leucocyte count and of the lymphocytes often follows a characteristic pattern This consists of occasional early leucopenia or more frequently, of normal leucocyte and differential count followed by leucocytosis due to relative and absolute lymphocytosis by the end of the first week of illness

In 115 cases personally reported in two groups the greatest leucocytosis occurred from the 16th to the 20th day of illness respectively with maximum average counts of 11,500 and 12 800 and with 70 and 69 per cent of lymphocytes The leucocyte counts tend to subside to normal in the third week following onset of illness although abnormal variation may persist for some months It is to be noted that the cases with highest maximum temperature reaction 103° F or above in 18 per cent of cases tend to show greatest leucocytosis and highest relative lymphocytosis Early leucopenia in an infection of undisclosed nature sometimes will be the first suggestive sign of infectious mononucleosis The variation in total leucocyte counts and in the time of development of lymphocytosis emphasizes the necessity of serial blood counts That the leucocyte behavior is not the individual s constant reaction to infection is shown by the records of numerous cases in which some other infection, such as tonsillitis, provoked the usual polymorphonuclear leucocytosis The characteristic blood morphology is described by Dr Downey in Part II of this chapter

The *sheep cell agglutination test* of Paul and Bunnell has been emphasized in reports since its notation by them and has, undoubtedly stimulated more wide spread interest in the disease In cases personally observed a high titer, 1 1,192 has always been associated with infectious mononucleosis On the other hand titers of 1 112 have not been distinctive and have been noted frequently in other types of infections Paul [8] believes that it is important to do absorption tests to differentiate the sheep cell agglutinins present in infectious mononucleosis from Forrsman antibody present in normal and in serum cases Emphasis of serial determinations is necessary, as the increased titer may not appear until during the second week of illness or later These agglutinins tend to disappear faster than those associated with virus diseases or with bacterial disease like typhoid fever Forty seven of 65 cases reported by Bernstein[4] had a positive agglutination of 1 160 or greater It may be safely said that the presence of the agglutinins in high titer definitely points to infectious mononucleosis However, in typical

diseases are characterized by adenopathy The lymph node would appear to be the habitat of the agent in infectious mononucleosis In the study of etiological agents broad biological concepts of possible agents should be entertained The frequency with which virus diseases have relative hymphocytosis would speak for possible virus etiology

Complications and Prognosis

It may be stated that uncomplicated cases recover quite universally Deaths referred to with lesions of the central nervous system may or may not be due to associated infections Suppurative adenitis is described and similar pyogenic infections suggest associated infections Rheumatic endocarditis has been noted following infectious mononucleosis Although the benignity of the process is apparent its morbidity and duration of illness justify careful observation and early diagnosis The longer duration of infectious mononucleosis compared to that of tonsillitis emphasizes the prognostic value of its recognition

Treatment

The treatment has been symptomatic and has been dictated by the type of local lesion in the throat and by the degree of the systemic reaction In addition to the general measures used in diseases with systemic febrile reaction, with attention to adequate fluids relief of headache and diffuse aching sensations local measures such as throat irrigations with normal saline may be used Convalescent serum has been used[3] and results were considered to be good The same observer noted some possible shortening of the course although no striking influence from the use of sulfonamide compounds In another report[3] some benefit was noted in subacute cases as measured by shortening of the course following the use of a sulfanilamide In a few personally observed cases which early in their course before diagnosis was established received therapy with one of the sulfa compounds in adequate dosage no favorable effect was noted The temperature in some instances continued on its upward swing during the 48 to 72 hour and sometimes longer period during which the drug was used The sulfonamide therapy apparently has been ineffective

considered In the latent period before lymphocytosis or localization of the infection in the throat has occurred the predominance of symptoms such as headaches, abdominal discomfort or muscle and joint pains has led to variable and sometimes uncertain or wrong conclusions Often the early course of the disease, when interpreted in view of the behavior of the blood counts, will suggest this entity and integrate the variable symptoms Early lymphadenopathy alone is suggestive of this entity The usual absence of severe degrees of prostration and of embolic phenomena should dictate conservatism as to prognosis until the process has declared itself From the standpoint of early recognition it is desirable to reemphasize that not infrequently a latent period, sometimes extending over two weeks, exists before lymphocytosis occurs In such cases tonsillitis or pharyngitis may supervene though relatively late Recognition of cases with systemic reaction only may be suggested first by the bizarre behavior of the leucocytes. Leucopenia and later leucocytosis and lymphocytosis suggest the condition before the development of physical signs, blood morphological changes and sheep cell agglutinins in high titer establishes the entity The necessity of repeated blood counts and study of blood morphology is apparent if such cases are to be recognized early and spared uncertain prognosis

Recently there have occurred under observation of the writer and other staff members cases with lymphocytosis, which do not satisfy the criteria of infectious mononucleosis but rather are comparable to those of infectious lymphocytosis described by Smith and others The cases have been of milder intensity than those of infectious mononucleosis For the most part these patients have been ambulatory and have had minor respiratory infections without the angina and characteristic adenopathy of infectious mononucleosis There has been absence of the blood picture of infectious mononucleosis, and the heterophile antibody has not been present in high dilutions It is interesting to note that the cases of infectious lymphocytosis occurred during the period that there was an epidemic of atypical pneumonia of unknown etiology, which also was associated frequently with relative lymphocytosis This common finding was impressive and might suggest a similar etiological agent

Leukemia may be excluded by hematological study The clinical features have not been confusing except in one early case Hodgkin s disease and other lymphogranulomata have not been confused and tuberculosis and suppurative adenitis have presented entirely different physical signs of infection in the lymph nodes and surrounding tissue

A disease, in which the blood picture may simulate leukemia suggests that the stimulus for both may vary more in degree than in inherent nature The throat lesion sometimes appearing as secondary to the period of systemic reaction is somewhat analogous to the mucous membrane lesion of secondary syphilis Both

features The cytoplasm tends to be increased in quantity in the larger forms and in basophilia in all In many cases the basophilia is equal to that of plasma cells, and the eccentric position and morphological pattern of the nuclei of some of these very basophilic cells indicate that they are intermediate between lymphocytes and plasma cells A few genuine plasma cells may be found also This tendency to form plasma cells has been noted by many and is described by Schwarz[4] as plasma cell metamorphosis" We referred to the intermediate forms as 'abortive plasma cells While completely differentiated plasma cells never are numerous, the lymphocytes show a decided tendency to develop in that direction

The cytoplasm of the atypical lymphocytes is composed of basophilic 'spongioplasm and yellowish hyaloplasm" (Wright s stain), and the two components are not evenly mixed The homogeneous hyaloplasm tends to collect about the nucleus and often forms a clear area at one side of the nucleus or in an indentation of the nucleus It also forms rounded vacuoles in the dense blue spongioplasm The latter is very abundant and very dense in the cells of some patients (our type I cases) In others (type II) the cytoplasm is paler because the spongioplasm is not as abundant or as dense and is confined to the periphery of the cell to basophilic streamers radiating from the nucleus or to one or two large, irregular bluish areas The cytoplasm may be very abundant in this type of cell and the nucleus plasma ratio therefore is greatly decreased Azuro philic granules may or may not be present in the cytoplasm of both the basophilic and paler cells Often the granules are coarser than those of normal lymphocytes The occurrence of azure granules in a very basophilic cytoplasm is quite unusual and therefore worthy of special note They do not occur in typical plasma cells of this or other diseases

The nuclei of the majority of these cells are identical with those of mature normal lymphocytes The chromatin is distributed in the form of dense cloudy masses which gradually fade into the parachromatin There is greater than nor mal condensation of chromatin in the nuclei of those cells that are developing to plasma cells and the plasma cell type of nucleus is reached in some instances The nucleus may be round, indented or lobulated the irregular nuclei seeming to be most frequent in the cells that are very basophilic

As it is difficult to describe these cells without illustrations reference should be made to the colored plate in our earlier publication[7] On account of the alarm ing clinical features in some patients recognition of the characteristics of these cells will help avoid a mistaken diagnosis of leukemia

In addition to the atypical cells described above one usually finds lymphocytes of normal structure and cells showing all gradations between them and the large pathological forms

PART II

HEMATOLOGICAL AND PATHOLOGICAL ASPECTS

By HAL DOWNEY

Blood Picture

Study of the morphology of the cells in blood smears of patients with this disease has established the fact that the blood picture usually is quite characteristic although not absolutely specific. All cases show relative and absolute lymphocytosis at the height of the disease and in some patients this persists for some weeks, months or years (Farley[33]) after clinical recovery. The moderate leukocytosis, which follows the early leukopenia of many cases, is due to increase in the number of lymphocytes and as this is accompanied by a decrease in the absolute number of granulocytes the relative increase of lymphocytes may be very high (92 per cent in one of our cases in which the total leukocyte count was 17 000). Schwarz[34] states that the lymphocytosis is preceded by a neutrophil leukocytosis in the earliest stages of the disease.

The lymphocytes usually are not the normal cells seen in the lymphocytosis of pertussis or the relative lymphocytosis of typhoid fever, measles, Banti's disease, etc. In infectious mononucleosis the majority are atypical, pathological, functionally active "leukocytoid", mature lymphocytes which exhibit many morphological variations. They have been described in detail and illustrated with colored figures by Sprunt and Evans[4] (1920), Downey and McKinlay[7] (1923), Baldridge, Rohner and Hansmann[3] (1926), Glanzmann[30] (1930), Schwarz[34] (1932) and Nyfeldt[11] (1932). Excellent photographs were published by Sundberg, who gave a detailed description of the morphological features of the disease.

In our earlier publication[7] (1923) we divided these cells into three types but attached no special significance to their occurrence on account of the numerous gradations between them, even in the same blood smear. However, we have noted repeatedly that the blood picture of a given case will be characterized by the predominance of lymphocytes of one of these types. These types of lymphocytes are illustrated on our colored plate[7].

Not all of the lymphocytes in any one blood smear conform to one of these types; in fact the lymphocytic picture is quite heterogeneous, a point to be kept in mind in distinguishing this blood picture from that of lymphatic leukemia. Small, medium and large forms are present, and most of them show atypical

in our series of 50 cases, but there is no doubt but that it occurs in rare instances This does not prove the presence of immature cells in the blood as has been claimed, for we know that any mature lymphocyte can divide, when it is located in the tissues lymph or serous fluid but not in the blood under normal conditions It is more likely that there has been some alteration of the blood plasma which favors mitosis Mitosis of blood lymphocytes rarely is seen in any condition except leukemia The possibility of its occurrence in infectious mononucleosis may be urged as one of the points of similarity between this disease and lymphatic leukemia

Many of the older writers believed the atypical pathological lymphocytes to be immature lymphocytes identical with the lymphoblasts of acute lymphatic leukemia and they found it difficult to distinguish between the early stages of this disease and acute leukemia That this difficulty has not yet been overcome completely is shown by the recent statements of Kracke and Garver[9] (1935) who write that it is generally believed that the predominating lymphoblasts appearing in both acute leukemia and infectious mononucleosis cannot be distinguished morphologically with certainty and of Leitner[10] (1935) who states that from the blood picture alone it is impossible to distinguish acute lymphatic leukemia from lymphatic reactions These statements obviously are based on incomplete knowledge of the morphology of lymphocytes

The confusion is in part due to the fact that the criteria used for judging the degree of maturity of lymphocytes are not always understood Some believe that any large basophilic lymphocyte is a lymphoblast while others seem to believe that the degree of basophilia of the cytoplasm is an expression of the age or maturity of a lymphocyte the more basophilic cells being the younger ones This is a theory advocated by Wiseman[11] and it has been followed by Stuart Burgess Lawson and Wellman[12], who have stated recently that the basophilic lymphocytes of our disease are immature

Leading hematologists agree that the nuclear pattern is the most reliable feature for estimating the stage of maturation of a cell for a given moment during the progress of its differentiation from a more primitive cell form The lymphoblasts of acute lymphatic leukemia have delicate "leptochromatic" nuclei in which the chromatin is evenly distributed in the form of delicate strands with rounded meshes which give the nucleus a sieve like appearance or the chromatin is in the form of a delicate stippling without any coarse aggregates except around the nucleoli As these cells begin to mature, the chromatin granules or strands become coarser and dense cloudy masses of chromatin appear which give the nucleus the characteristic "pachychromatic" structure of the mature cells

As judged by nuclear structure the majority of the lymphocytes of infectious mononucleosis are mature cells and if the tendency to form plasma cells

Monocytes usually do not participate in the reaction, and it is clear that the pathological cells, which give the blood picture its character, are mature lymphocytes which have undergone functional alteration Occasionally one encounters a patient in whom the monocytes show about the same "leukocytoid" changes as those noted for the lymphocytes The nucleus may retain its specific monocytic character, but the cytoplasm is blue and more basophilic than in the normal monocyte, and the azurophilic granules are coarse and distinct Glanzmann[36] describes monocytoid cells and monoblasts He believes that they occur in the early stages of the disease, and that they are derived from desquamated littoral cells of lymph node sinuses at the time the infective agent is draining into the node

Nyfeldt[11] described cells that are intermediate between lymphocytes and monocytes and believed this to be good evidence for his view of the origin of monocytes from lymphocytes Schwarz[34] interpreted these same cells as indicating that the cells of the reticulum, from which both lymphocytes and monocytes are derived have attempted to develop in the two directions at the same time

The one case of our series, which had many monocytoid cells in the blood, was in the late stages of the disease, and a biopsied lymph node showed no indication of the development of monocytes from sinus reticulum Usually the monocytes are not involved, and the term "mononucleosis" must not be interpreted as referring to genuine monocytes

The granulocytes, particularly the neutrophils are reduced in absolute number and sometimes this reduction is so pronounced that a condition of agranulocytosis is approached during the early leukopenic stage The neutrophils usually contain dark, 'toxic', neutrophil granules and sometimes, vacuoles in the cytoplasm, and the nucleus may show some signs of pycnosis These are the toxic neutrophils so common to infectious diseases There is "shift to the left in the Schilling sense with many 'stab forms and sometimes with myelocytes The presence of the latter and of infrequent normoblasts indicates bone marrow irritation which however probably is secondary to the pathological processes taking place in the lymph nodes where the infective agent seems to have its primary location This bone marrow response during the course of the illness together with the fact that the disease begins with a neutrophil leukocytosis (Schwarz[34] and Whitby and Britton[38]) and that before and after attacks there is reaction to other types of infection with the usual neutrophil leukocytosis indicates that the lymphatic reaction, which characterizes this disease, is not a vicarious reaction due to constitutional weakness of the myeloid system

Mitotic figures in the lymphocytes of the blood have been described and figured by Schwarz[34] and others and in the case described by Angelini[72] some of the plasma cells were seen to be in mitotic division We have not observed this

nucleosis and the "monocytes" of the blood as pathological lymphocytes which is the conclusion of most recent writers on the subject. Gingold[18] however believes that monocytic angina exists as a system affection of the reticulo-endothelial tissue, and that it is not the same disease as infectious mononucleosis. The chief distinction is that the blood contains many genuine monocytes rather than the monocytoid lymphocytes interpreted as monocytes by many authors. We have not encountered a case that could be included in this group.

Israels [1] also seems to believe that some relationship exists between infectious mononucleosis and monocytic leukemia. He described a case of the former which he interpreted as being intermediate between a typical case and one of genuine monocytic leukemia. He sees immature monocytes as well as abnormal lymphocytes in the blood of typical cases of infectious mononucleosis.

Cases of infectious lymphocytosis in children having blood pictures somewhat similar to chronic lymphatic leukemia recently have been reported by Reyersbach and Lenert [2] and by Smith [3]. The 16 children reported by the former authors were receiving convalescent care following rheumatic fever and were believed to have infectious mononucleosis without symptoms although the Paul and Bunnell test was negative and there were no lymphocytes similar to those of infectious mononucleosis. Leukocyte counts of from 18,400 to 59,300 with 79 to 93 per cent lymphocytes were encountered. Most of the lymphocytes were small normal cells and there were no lymphoblasts.

Smith also reported cases that seem to belong in this group and which might be mistaken for either infectious mononucleosis or lymphatic leukemia. Some of the cases were acute and were not associated with recognizable signs or symptoms; others followed infection of the upper respiratory tract. The lymphocytes of both groups were mainly of the small variety which had more basophilic cytoplasm than normal lymphocytes. Up to 5 per cent of large lymphocytes with narrow basophilic cytoplasm were seen but there were no cells of the infectious mononucleosis type. In the two acute cases reported the maximum leukocyte counts were 44,300 and 98,000 with 79 and 86 per cent lymphocytes respectively. The heterophil agglutination test was negative in all 11 cases. The monotonous lymphocytic blood picture of these cases resembled that of chronic lymphatic leukemia as it is seen in adults rather than infectious mononucleosis.

Usually the blood picture of infectious mononucleosis is quite characteristic but not absolutely specific for this disease. We have seen 2 cases of agranulocytosis and one of septicemia with this type of lymphocytosis. Of the 2 cases of agranulocytosis the one which terminated fatally with a leukocyte count of 800 began with a count of 15,000 and a high percentage of leukocytoid lymphocytes. The other patient did not have the high initial count and the lowest total count

can be regarded as a ripening or maturing process, many of them are over ripe The increased basophilia, increased amount of hyaloplasm and lobulation of the nucleus represent functional alterations that are not concerned with the degree of maturity of the cells

Cells with immature, leptochromatic nuclei are seen occasionally, and we described such a case in our earlier series and illustrated the cells on our colored plate[7] These cells were not sufficiently immature to be called lymphoblasts, but their nuclei showed more diffuse distribution of the chromatin than is seen in the mature cells Their cytoplasm was abundant and showed the usual basophilia and increased hyaloplasm These are the most immature cells encountered in our larger series of 50 cases However, cells that are only slightly immature have been seen frequently These immature cells are not identical with those seen in acute lymphatic leukemia, they usually show the functional alterations of the cytoplasm, and their nuclear structure indicates that they have been derived from the reticulum and have retained some of the characteristics of the nuclei of reticulum cells This will be explained below in the section on the pathology of the lymph nodes

The splendid illustrations in the monograph of Schwarz[34] prove that genuine lymphoblasts as immature as any seen in acute lymphatic leukemia may occur in rare instances Glanzmann[30], Nyfeldt[11] and others also claim to have seen such cells and state that they are never numerous On account of the occasional presence of a limited number of these cells Schwarz[34] feels that there might be difficulties in distinguishing some early cases fram acute leukemia Cells of this type probably do not exist in normal human lymph nodes (Downey[44 45 46 47]), so their occasional presence in the blood of infectious mononucleosis is of great theoretical interest In the case referred to in our earlier series a few of the immature lymphocytes contained Auer bodies in their cytoplasm, and a similar observation was made by Schwarz[34] These structures are regarded as being specific for leukemic blood

The lymphocytes of a few cases of infectious mononucleosis which we have seen are normal mature cells, which do not show the functional, "leukocytoid" alterations described above Such a blood picture might be confused with that of chronic lymphatic leukemia if the history were not known

The distinction between this disease and leukemia and certain similarities in the pathological picture have been discussed by Downey[7 50] and Emil Schwarz[34] among others Gingold[48] believed the disease to be related closely to leukemia, considering it to be the benign form of acute subleukemic or aleukemic lymphatic leukemia and the monocytic angina of Schultz[49] to be the benign form of monocytic leukemia of reticular origin

Schultz later interpreted his monocytic angina as a type of infectious mono-

rounding up of groups of cells of the reticulum which however is not specifically related to sinus reticulum as claimed by Gall and Stout[3]. Many of these cells acquire basophilic cytoplasm and some of them separate from the group and transform to lymphocytes. The transformation of reticulum cells to lymphocytes is seen best in imprints of the nodes which will be described later.

That the nodules of reticulum cells are not specific for infectious mononucleosis is shown by the work of Nishii who saw similar structures in the regional lymph nodes of guinea pigs after subcutaneous reinjections of *Staphylococcus pyogenes aureus* of weak virulence. He interpreted them as the expression of an immune reaction of the sensitized organism.

All of the nodes removed at the height of the disease are hyperplastic and lymphocytes, general reticulum and sinus reticulum are involved in the process. There is great variation in the degree of involvement of these different constituents of the nodes even in different parts of the same node. The degree of hyperplasia is never as extensive or as uniform as in advanced cases of lymphatic leukemia and there is no invasion of the capsule by the lymphocytes of the nodes. Large germ centers and follicles were seen in only one of the nodes and this was removed very early in the course of the illness. The other nodes showed only remnants of follicles and germ centers or none at all. A portion of one of the nodes was of normal structure and contained follicles with germ centers, the greater portion of the node was very hyperplastic.

Cortex and medulla cannot be recognized in the nodes showing the most advanced pathological alteration. Sinuses may be filled with cells of the reticulum but can be recognized or they are completely obliterated by the hyperplastic reticulum and lymphocytes. Dense masses of small lymphocytes of uniform size and structure seem to be rather characteristic. They are generally in the interior of the node so probably do not represent enlarged follicles. They alternate with looser areas in which the reticulum is conspicuous and in which the lymphocytes show great variation in size and structure. It is here and in the sinuses that one sees the atypical basophilic large lymphocytes sometimes with lobulated nuclei that seem to be identical with similar cells in the circulating blood. Even in the sections one can note transitions between these cells and normal lymphocytes. Groups of plasma cells are encountered also in all the nodes. The nodules of reticulum cells can be seen in these looser areas and also in the dense areas of small lymphocytes but never in the sinuses as claimed by Gall and Stout.

The great variation in structure and degree of involvement of the different constituents of the nodes indicates nonspecific reaction to some infective agent (virus?) located within the nodes (Glanzmann[16]). The extreme increase in the number of lymphocytes could not be accounted for if toxic material were merely draining into the nodes from some distant focus. However the extreme

was 1 400 There were no granulocytes in the blood smears for three successive days The lymphocytes were mostly large, basophilic, stimulation forms similar to those of infectious mononucleosis

The granulocytes do not disappear from the blood in infectious mononucleosis, and their reduction in number is more than compensated by the absolute lymphocytosis The condition gives a good illustration of the general rule that lymphotropic agents depress the granulocytic system, discussed recently by Wiseman, Doan and Erf[4]

Lymph Nodes

Lymph nodes have been removed for biopsy at some time during the progress of the disease by several investigators Marked differences of opinion regarding the pathological alterations to be seen have resulted from these studies A series of nodes removed from 8 different patients studied recently by Downey and Stasney [4] has shown that the severity of the disease and the time of removal during its progress are important factors in determining the pathological picture Nearly all the pathological features previously described could be seen in this series

Nearly all authors report more or less complete loss of normal lymph node structure and hyperplasia of lymphatic tissue that may approach that seen in nodes from lymphatic leukemia This hyperplasia may include marked enlargement of germ centers (Longcope[6], Baldridge Rohner and Hansmann[35] Nelken [5], Glanzmann[36] Marchal Bargeton and Mahoudeau [6] Gall and Stout [7]), or germ centers and follicles may be lacking (McLean [8], Vogl [9])

Fox[60] reported hyperplasia of both reticulum and lymphocytes with an attempt to retain the architecture of the node Nelken , Fox[60] Hartwich[61] and Vogl [9] described the picture as that of a nonspecific lymphadenitis An increase in the amount of general reticulum has been mentioned by several authors while others have noted marked hyperplasia of sinus reticulum which occurs in the early stages of the disease according to Glanzmann[36] Pratt[1] described the formation of dense foci of reticulum cells scattered through the nodes in such a way that they give the sections a spotty appearance Gall and Stout[7] state that these nodular masses of reticulum cells are derived from proliferating cells of the sinus walls which may extend into the parenchyme and become isolated Four of the nodes studied by Downey and Stasney[14] were removed at the peak of the disease and the other four either early or late Sections from all nodes showed the dense foci of reticulum cells making this feature about the most constant part of the picture

The small nodules of reticulum cells are produced by the proliferation and

identical with the lymphoblasts of acute lymphatic leukemia which may have the structure of myeloblasts if sufficiently immature Cells of the latter type have been described and illustrated by Schwarz[74], but they have never been seen in our series either in the blood or the imprints The immature lymphocytes which we have seen are the ones described above that are derived from the reticulum

The shift to the left seen in the increased development of lymphocytes from the reticulum is a condition similar to that seen in lymphatic leukemia (Jaffe[64] [66] Semsroth[97] Stasney and Downey[4]) and leukemic reticulosis However, *in these diseases most of the lymphoid cells remain undifferentiated* and reach the blood stream in this condition while in infectious mononucleosis the *blood smears contain few or no immature cells* Maturation of lymphocytes is therefore very rapid and complete in spite of the activation of the lymphatic tissue by the infective agent

Incompletely developed plasma cells are found in the blood smears of most cases of infectious mononucleosis and this tendency to form plasma cells is one of the characteristic features of the blood Completely developed plasma cells are more numerous in the imprints than in the blood and the imprints also show many transitional stages between plasma cells lymphocytes and reticulum cells The blood smears show that these cells can be delivered to the blood in any stage of their development If plasma cell formation can be regarded as a process of ripening or maturing we must conclude that the lymphotropic virus of infectious mononucleosis stimulates both the development and the maturation of the lymphocytes The reaction is therefore quite different from that seen in lymphatic leukemia in its acute form which is characterized by the failure of the cells to differentiate In infectious mononucleosis there is stimulation of development but no interference with differentiation

Downey [4] (1927) has shown that in normal lymph nodes the regeneration of lymphocytes differs from the leukemic process in that the lymphocytes derived from the reticulum do not pass through the lymphoblast stage a stage in which the young lymphocytes are identical with myeloblasts Under normal conditions the differentiation is more direct and abrupt The leukemic lymphoblasts are derived also from the reticulum but they remain in the undifferentiated condition longer than do the lymphocytes of normal nodes (Fineman[8] 1922 Stasney and Downey[8] 1935)

The hyperplastic condition of the nodes in infectious mononucleosis indicates that regeneration is very rapid and so one might expect to find lymphoblasts of the leukemic type Their practical absence and the presence of numerous direct transitions between reticulum and lymphocytes indicate that regeneration is proceeding along normal lines However the occasional finding of lymphoblasts

hyperplasia of sinus reticulum in some of the nodes indicates that this may occur also

Imprints of the nodes stained with May Grunwald Giemsa furnish the best material for study of their detailed cytology Scrapings of the fresh nodes can be stained also supravitally, as was done by McLean [8], who found many rosette cells and a few clasmatocytes in addition to the numerous small lymphocytes. In dry films stained with Giemsa he noted many large cells with pale nuclei having nucleoli and finely stippled chromatin These cells were considered to be lymphoblasts Nyfeldt[11] also made supravital studies of the nodes and noted the same atypical cells that were seen in the blood and transitions between lymphocytes and monocytes which he also thought he could see in the blood smears

Imprints were made of the eight nodes studied by Downey and Stasney[4] The large atypical, leukocytoid lymphocytes, so characteristic of the blood smears, were also numerous in the imprints, proving that these atypical lymphocytes are formed in the nodes In one patient of this series most of the lymphocytes of the blood were of the pathological type, while only a few such cells were found in the imprints of his node, despite the fact that this node showed the most advanced pathological changes This shows that the pathological alteration of the lymphocytes may take place after they have reached the blood stream Usually there was good correlation between the number of pathological cells in the blood and the number of such cells in the imprints

The imprints contained many transitional stages between normal lymphocytes and the pathological forms Cells of the reticulum were rather numerous in the imprints as were also many transitional stages between them and lymphocytes The details are discussed and illustrated by Downey and Stasney[4] The cells of the reticulum, as seen in the imprints, have very characteristic nuclei with thin membranes, finely stippled chromatin and irregular pale nucleoli As the cells differentiate to lymphocytes, the nuclei are gradually transformed to the type that is characteristic of the lymphocyte Many large basophilic cells with such intermediate nuclei are seen in the imprints indicating that the basophilic, leukocytoid alteration of the cytoplasm may be developed at any stage during the maturation of the lymphocyte as it develops from the reticulum

Lymphocytes with immature nuclei showing some of the characters of the nuclei of reticulum cells are more numerous in these imprints than they are in those from normal human nodes, proving that heteroplastic development of lymphocytes from the reticulum is accentuated in infectious mononucleosis The homoplastic form of regeneration is not replaced, however, as is shown by the numerous mitotic figures in lymphocytes

Lymphocytes that are derived from the reticulum may escape to the blood stream before their nucleus has reached complete maturity These cells are not

he same patient He believes that these two cases prove that only the lymphatic nodules present in normal marrow participate in the reaction of rubeola and infectious *mononucleosis and that this explains the negative findings in the marrows* of most cases of infectious mononucleosis

A recent patient in the University of Minnesota Hospitals had hyperplastic marrow which contained many lymphocytes and infectious mononucleosis cells The patient was twenty one years old His heterophil agglutination test was positive in a dilution of 1 1 792 His leukocyte count was 22,400 with 87 per cent lymphocytes on the fourteenth day of illness which was the day of the bone marrow aspiration The myeloid erythroid layer was 18 5 per cent by the *Schleicher Scharp technique which is three to four times the normal value* A differential count based on 1 500 cells done by R H and D S Reiff showed 29 5 per cent of lymphocytes of all types and of these 15 4 per cent were the *atypical infectious mononucleosis* types *of lymphocytes similar to those of the* blood

A lymph nodule was not aspirated from this marrow but it might be assumed that marrow from the immediate vicinity of such a nodule was included Marrow from another case showed only a myeloid reaction with rather marked shift to the left in the granulocyte series As the preparations were made by the direct smear method there was no way of estimating the degree of hyperplasia of this marrow

The spleen is enlarged in 50 per cent or more of the patients with this disease and so might be assumed to be involved In one of Moeschlin s [1] patients the organ was large enough to be punctured Smears were made from small aspirated fragments which contained little blood A *differential* count gave 12 per cent infectious mononucleosis cells similar to those of the blood and of aspirated material from a lymph node From this and his previous observations the author concludes that all the lymphatic tissue of the body including that of the spleen and marrow reacts in this disease

of the leukemic type in the blood smears by Schwarz[34] and others points to the possibility of the other type of regeneration in a few, very severe cases

It has been shown that infectious mononucleosis differs from lymphatic leukemia in several respects However, on account of the occasional presence of very immature lymphocytes in the blood, Schwarz[34] believes some early cases might be difficult to diagnose Usually the pronounced 'leukocytoid' characters of the lymphocytes will enable one to distinguish such a case from one of acute lymphatic leukemia A biopsied lymph node would show greater polymorphism *of cells and less uniformity of structure than would be seen in a leukemic node*

The blood picture and the marked reaction of lymph nodes, which is characteristic in so far as the production of the atypical lymphocytes is concerned, and the marked shift to the left in lymphocyte regeneration indicate that the disease is caused by some specific infection and is not dependent on a peculiar constitution with weakness of the granulocytic system as was believed by Turk That these patients react to other types of infection with a neutrophil leukocytosis is further proof for this view which is in agreement with the conclusion of Schwarz[34], Glanzmann[36] and many others

Bone Marrow and Spleen

Sternal biopsies have been done on many patients with infectious mononucleosis Schulten[73] Klima[74] Nordenson[7], Henning and Keilhack[6] and formerly Rohr failed to find any increase in the number of infectious mononucleosis cells beyond what could be expected from the amount of blood contaminating the preparations The positive findings of Young and Osgood[8], Freeman[9] and Markoff were interpreted by Rohr[77] as being due to the admixture of blood with the marrow However in one recent case (1940) Rohr[7] noted marked lymphatic hyperplasia in a smear of pure marrow and concluded from this that the lymphatic portion of the marrow (the lymph nodules found in the marrow by Rohr Moeschlin and many others) may be involved in the disease and that this portion might be punctured in obtaining the marrow

Later (1941) more detail concerning the marrow of this case was given by Moeschlin[81] who stated that it was the only one of a series of 43 in which sternal aspirations were done that showed an increase of the infectious mononucleosis cells The smears were made from pure marrow with no admixture of blood A *myelogram showed 15 per cent small* lymphocytes and 8 per cent of the atypical lymphocytes similar to those of the blood Moeschlin[81] believes this increase of marrow lymphocytes to be analogous to his previous observations in the marrow of a case of rubeola in which a marrow lymph nodule was aspirated and showed the same plasma cell reaction as an aspiration of a lymph node from

he same patient He believes that these two cases prove that only the lymphatic nodules present in normal marrow participate in the reaction of rubeola and infectious mononucleosis and that this explains the negative findings in the marrows of most cases of infectious mononucleosis

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March 1 1944

CHAPTER XX

MEASLES

By HAROLD L HIGGINS

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Introduction

Measles is an acute infectious disease There are general constitutional symptoms of fever and toxicity but the most characteristic features of the disease are the enanthem, or eruption on the mucous membranes and the exanthem or eruption on the skin these eruptions are the main points in recognizing or diagnosing the disease The enanthem is seen in the cheek as Koplik spots, it also exists in most if not all of the mucous membranes of the body, the reactions to irritation of the mucous membranes probably are responsible for the marked symptoms of coryza bronchitis and conjunctivitis as well as the less striking signs of diarrhea vaginitis pyelitis and endometritis. Lymphadenitis is present also

There is an *incubation period* of 10 to 15 days between the time of getting the infection and the occurrence of the characteristic symptoms, during this period the patient usually feels quite well Then the *invasion period* begins

and the symptoms of fever, malaise, conjunctivitis and coryza appear, the Koplik spots usually are present at this stage After 2 to 4 days, the period of eruption begins, and the characteristic rash appears on the skin, this lasts 3 to 5 days The fever and symptoms in the uncomplicated case subside in 2 to 3 days and aside from the mild respiratory symptoms and a fading rash, the patient feels well again There then may follow complications, due to the secondary invading organisms, which either are picked up during the illness or were present previously, the patient being a carrier or having a chronic infection

Etiology

The etiological agent of measles still is unknown or at least not definitely proven Clinical evidence justifies the conclusion that the contagium of the disease is present in the respiratory secretions from the onset of the coryza and fever until the rash begins to fade, it does not seem to be present during the incubation period nor during complications following measles Clinical deductions suggest also that it is present simultaneously in other body excretions the urine, the feces and the sweat It is present in the blood during the course of the disease and during the incubation period, a blood transfusion from a donor, who was in the incubation stage of measles, has been followed by measles in the recipient thirteen days later The contagium would seem to be short lived outside the body, for measles is seldom transmitted other than by close contact between the patient and the person infected Healthy carriers of the contagium of measles do not seem to exist Some animals and birds are known to have illnesses suggesting measles following exposure to a patient, but there is certainly no evidence that they play a rôle in the spread of the disease In a hospital measles may spread occasionally from a patient in one room to one in a nearby room, although there has been no contact except through a third person

In summarizing the clinical data, one may conclude that the contagium of measles probably is transmitted mainly by droplets from the coughing crying sneezing or talking child probably it is growing in the blood of the infected person for a period of about 10 days, when it quite suddenly produces a toxin, which in turn produces the enanthem and constitutional symptoms, at the same time the infecting organism is excreted through the mucous membranes especially into the respiratory tract by six days later, the organism has been destroyed by the body defenses and is no longer present in the patient, the contagium also is short lived outside the body One may deduce from the clinical facts that there is possibly a transmutation of characteristics of the organism occurring in the body at the time of the onset of the symptoms of the disease

Many attempts have been made to find the causing organism of measles,

many of these including the non hemolytic coccus (streptococcus or diplococcus) producing a soluble toxin studied by Tunnicliffe Caronia Ferry and Fisher now are believed to be secondary invaders The present trend of opinion is that measles is caused by a filterable virus not yet satisfactorily identified Inclusion bodies fitting in with a virus origin however have not been demon strated conclusively in the epithelial cells in measles.

Epidemiology

Measles is one of the most widely disseminated of all diseases being found in practically all countries of the temperate zones It is endemic in the larger cities and centers of population At interval an epidemic will break out Re cently in New York these epidemics have been appearing regularly every two years During an epidemic those who have never had measles are very likely to contract the disease as most adults will have had the disease, those who get it are mainly children in the lower grades of school and younger children in their families Babies under six months of age ordinarily do not contract measles this immunity has been obtained from their mothers, for babies whose mothers have never had measles are susceptible

Epidemics of measles are not so frequent in the smaller towns and villages In the mountain and country districts many of the adult population have never had the disease this was demonstrated by the epidemics of measles in the camps in the recent World War, the patients being largely from the country troops

In communities where measles is not endemic and where most of the popula tion or their ancestors have not had measles an epidemic is likely to prove very severe and cause many fatalities such was the case in the Faroe Islands where one epidemic occurred in 1846 and the next in 1875 A community which is isolated and at considerable distance from other places similarly escapes epi demics of all the contagious respiratory infections But modern rapid transit by railroad automobile and airship is certain to cause individual epidemics to be more widespread and to come at more frequent intervals The long incuba tion period of measles and the extreme susceptibility of those not protected by a previous attack make it possible for the disease to be carried between widely separated points and readily to become implanted in a new environment When once introduced into a new locality it is almost impossible to prevent its spread

Epidemics of measles are most common during the winter and spring (January to June) they rarely occur in the summer and only occasionally in the fall An epidemic may be said to continue as long as there are susceptible individuals it gradually wears itself out and seldom persists after July first

The severity of a winter's epidemic usually may be foretold by the date of the first influx of cases, if it comes in January, one feels surer of a more extensive epidemic than if the first cases are in March

Immunity

There is no permanent natural immunity to measles Babies under six months of age whose mothers have had measles, usually are immune, but this immunity is lost rapidly after the child is six months old Boys and girls old people and young people are equally susceptible, if they have never had the disease The health or nutrition of the individual seems to have no bearing on the susceptibility to the disease

There may be a temporary immunity to measles It is hard to explain in any other way the development of an attack in a middle aged adult living in a city Such instances occur but seldom, chances of previous opportunity for infection being overwhelming

An attack of measles, however, confers an immunity which in the great majority of instances is complete against subsequent attacks Second, third and even fourth attacks have been reported The majority of these will not bear careful analysis Absolute reliance cannot be placed upon the statement of patients and relatives in regard to infectious disease Unfortunately the diagnosis of many physicians cannot be relied upon With due consideration to all of these arguments, however, it appears that with some people immunity after measles may not be complete, for there are quite a number of instances of second and even third attacks reported by competent observers, who have themselves seen all of the attacks Occasionally this failure to obtain immunity from measles following an attack of the disease appears to be an inherited or familial trait One family is reported, four members of which have had repeated attacks of measles, as vouched for by competent diagnosticians

Production of Passive Immunity

Methods of producing an immunity against measles are becoming practicable Passive immunity may be given to a susceptible individual by the injection of some blood serum or whole blood of a person who has had measles. This procedure has proven successful in practice, the success may be explained theoretically by the presence of antibodies in the blood of the patient who has recovered from the disease The potency of a donor's serum may be measured only by its ability to protect a non immune person against the disease, the following two statements seem justified from the recorded observations (1) The

maximum quantity of anti bodies is present about 7 to 10 days following the disappearance of the rash (2) Individuals differ in the quantity of anti bodies in their blood Sera from two individuals withdrawn at the same period in their convalescence may vary strikingly in their protective potency In practical application, it is the custom of some workers to pool the measles sera in order to get a fairly constant potency The preferable serum is that from the blood of a patient convalescing or recently convalescent from measles Unless the serum is to be used immediately, some preservative (as tricresol 0 5 per cent) is added An intramuscular injection of three to five c c of convalescent measles serum will protect approximately 66 per cent to 100 per cent. of susceptible individuals who have been exposed to measles within 4 to 5 days Ten to fifteen c c of serum of persons, who have had measles sometime previously, have the same protective power If the time of the exposure were more than 5 days and less than 8 days previously, an attenuated or afebrile measles would follow in approximately the same percentage of cases no distinct protection usually follows this dose after the 8th day Passive immunity obtained in this manner is not permanent, how long it lasts varies with the individual person and may be for as short a period as two weeks Passive immunity to measles by this method is comparable to the immunity to tetanus diphtheria or scarlet fever conferred by the respective antitoxins against these diseases the protection being of short duration Human immune globulin extracted from human placentas also has been found to give passive immunity to patients exposed to measles The use of this is described in the section on Treatment to be found on a later page of this chapter

Production of Active Immunity

Active immunity is that given by the disease itself, or by the organisms or toxins causing the disease The giving of convalescent serum on the sixth or seventh day following the infection may result in an attenuated or afebrile measles which probably confers a permanent immunity There have been attempts to produce a permanent immunity in babies under five months of age and still protected by anti bodies from the mother by swabbing their noses with the nasal discharges of measles patients In practice neither this latter procedure nor deliberate exposure of a person to measles to build up active immunity, though the patient receives convalescent serum should be regarded as safe or advisable The attempt to attenuate the disease by convalescent serum in a child already exposed is, however a sound and safe procedure If the identity of the contagium of measles shall become established definitely and it seems quite possible that it shortly may be practical methods of obtaining an active immunity doubtless will be developed

Pathology

The described pathological changes in measles itself are confined to the skin. At the site of the macular eruption of measles, there is an exudation of serum with leucocytes and occasional red blood cells into the corium, these elements force their way into the epidermis, as a result the cells of the epidermis are forced apart and minute vesicles or pustules are formed. The epithelial cells themselves undergo degeneration and are phagocytized by the wandering leucocytes. There is also some proliferation of epithelial cells. In the corium there is an accumulation of leucocytes, especially around the blood vessels of the papillæ, the hair follicles and the sebaceous glands. Eventually the exudate is absorbed, the accumulation of cells in the epidermis are desquamated, and the cellular infiltration in the skin disappears. The lesions in the mucous membranes probably are quite similar in nature. There are also the changes in the body due to toxins and fever such as a cloudy swelling of the parenchymatous organs.

The findings post mortem in a death from measles are almost invariably the result of complications. In the secondary pneumonia following measles there may be found any or several of a variety of organisms, especially pneumococci, streptococci and influenza bacilli. Streptococcus hemolyticus often has been the only organism found. The pathology is more marked often in the walls of the bronchi and interstitial tissue than in the alveoli. As with any type of secondary pneumonia the character and extent may vary with the individual case, from slight involvement to a massive consolidation, even with pleurisy and empyema. A prevailing type of secondary invading organism in a certain epidemic or season frequently causes a definite type of pathology in the patients with pneumonia.

Incubation Period

The incubation period, that is the time elapsing between exposure and manifestation of any symptoms, usually is ten or eleven days; the extreme limits have been reported as eight and twenty days, but less than nine or over fifteen days are very exceptional. Generally there are no symptoms during this period.

In certain cases where the incubation period of measles has been passed in a hospital, and frequent records of body temperature have been taken, an otherwise unexplained fever even up to 102° F has been noticed occasionally.

Symptoms

The *onset* of symptoms in measles is gradual over a period of two or three days. The fever rises gradually; there is seldom a distinct chill. Vomiting is

small children occurs but is rare in the older child or adult in this regard it is in contrast to scarlet fever, where vomiting at the onset is present in about 80 per cent of cases Convulsions may occur occasionally at the onset in a young child

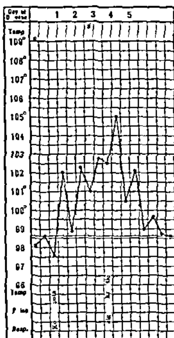


FIG 1 —Measles Frank case usual type Child 2½ years.

The *temperature* usually rises with the onset of the invasion period The temperature curve usually shows an up and down course with variations during the day of one or two degrees, the direction of the curve is upward, however the total net rise each day being 1 to 2 degrees until the maximum is reached this is when the rash becomes full blown about one day after the first appearance, the temperature fall is also gradual but about twice as rapid as the rise In the uncomplicated case the temperature usually is normal by the fourth day of the rash, at which time the rash is rapidly fading A temperature elevation beyond this time usually means a complication

The *respiratory symptoms* of measles are quite characteristic and uniform The symptoms are first those of a severe cold with rhinopharyngitis, shortly the signs of conjunctivitis laryngitis bronchitis and sinusitis become manifest

The *eyes* gradually become red and watery By the time of the onset of the rash the eyes are distinctly bloodshot With the conjunctivitis there is a mild photophobia the patient much prefers a darkened room A slight mucous crusting discharge will accumulate in the corner of the eyes The conjunctivitis clears up with the fading of the rash

The *rhinitis* follows the usual course seen in the common cold first with sneezing then edema of the mucous membranes with the stoppage of the nasal passages and then the discharge in turn serous mucous and finally if there are secondary pyogenic organisms in the nasal sinuses muco-purulent The nasal mucous membrane becomes quite red Occasionally epistaxis occurs

The *pharyngitis* is seldom so severe as to make swallowing difficult but the subjective symptoms of dryness rawness and scratchiness occur Examination of the throat will show at first a rough appearance the mucous membrane losing its usual smoothness minute vesicles may be seen on the soft palate and uvula preceding the roughening of the membranes The throat is red The tonsils and adenoid tissue are swollen usually no exudate is apparent on the tonsils.

The *voice* usually becomes husky, and hoarseness develops to a varying degree There may develop sufficient edema of the *larynx* to cause croup, in rare instances intubation or tracheotomy becomes necessary This latter condition, however, seems only to occur in a larynx previously infected, or as the result of a secondary invading organism, possibly the diphtheria bacillus. *Tracheitis* and *bronchitis* are present in nearly every patient and also disappear with the fading of the eruption Physical examination of the chest may disclose rales of all sorts, loud transmitted rales heard equally well all over the chest fine crackling or musical rales of bronchitis more localized.

Coughing begins shortly after the onset of the symptoms and continues at frequent intervals throughout the course of the disease It may become paroxysmal in type The coughing ceases as the inflammation of the respiratory tract clears up, persistence of the cough suggests complications

The symptoms from the irritation from the enanthem on the other mucous membranes usually reach their maximum with the appearance of the rash Thus vomiting, diarrhea, or colicy pains in the intestines, or burning in the vagina, or pain on urination may occur

About the third or fourth day of the symptoms, the characteristic *rash* of measles appears It is first seen just below the hair line on the back of the neck and on the forehead The lesions at first are small red macules about the size of the head of a pin, later they may coalesce to form larger and irregularly outlined macules The eruption rapidly spreads over the face and body It reaches its height in about 24 hours after its first appearance The intensity of the eruption will vary in different patients In some, it is of so slight an extent as to raise some doubt as to its diagnosis, in other patients, it is widespread and the lesions so confluent that large areas of skin are covered completely The entire skin, including the palms and soles, may show the eruption But however confluent the eruption, it still has a blotchy, irregular appearance, characteristic of measles, and is not symmetrical as in scarlet fever In the mildly and in the severely sick patient, the eruption may not be very prominent. After two days the eruption begins to fade its reddish appearance changes to a copper color, five days after the eruption began usually it has vanished to casual inspection, it may be evident on vasodilation of the skin as during a warm bath or under ultraviolet lamp for several days longer

Afebrile Measles

An afebrile type of measles may occur, this is ordinarily seen in patients given convalescent serum several days after the infection in these cases the toxic manifestations and the coryza are but slight, the eruption is not intense, but usually quite distinct. The body temperature may not rise above 100° F

Severe Measles

Measles may be severe by reason of the nature of the attack itself, or what is much more common, from the early onset of the complications

The uncomplicated severe cases occur either in younger children especially those badly nourished, or in older children and adults, whose general health has been affected by previous illnesses or by undernutrition, such as occurs in time of war Even from the beginning, the prostration is extreme, nervous symptoms are marked and the circulation is depressed as indicated by the cold cyanotic extremities and weak pulse The eruption is delayed Even these cases usually will get well if no complications occur

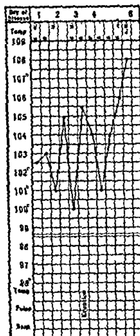


Fig 2 —Measles with fatal pneumonia (capillary bronchitis) developing with the appearance of the eruption Death Child 8 months.

In some children the pulmonary symptoms are severe from the start The laryngitis and bronchitis are marked and respiration labored The temperature is very high (104° to 106° F), and fine moist rales are heard all over the chest The eruption is scanty Cyanosis is present to a greater or less degree Convulsions may occur The symptoms are those of that type of pneumonia called capillary bronchitis This type of disease is particularly fatal Death may occur even before the eruption is apparent.

Hemorrhagic Measles

This form, under the name of black measles occupies a prominent place in the older descriptions of the disease It is fortunately very rare nowadays It is not to be confused with measles in which there is merely a moderate effusion of blood into the skin which is not uncommon nor of serious importance In hemorrhagic measles there were also hemorrhages into and from the mucous membranes as well as into the skin The patient with hemorrhagic measles usually is very sick, the mortality rate is high

Diagnosis

The diagnosis of measles is made from the history of exposure the catarrhal symptoms of invasion, Koplik spots rash, adenitis and leucocyte count

Koplik spots are white, granular particles about the size of a small grain of salt a red area surrounds each spot, and the spot is about the size of the head of a common pin Koplik spots vary in number in the different cases, if only two or three are apparent, they are found usually on the buccal surface opposite the upper, second, deciduous, molar teeth (or in older children and adults the upper second bicuspids) As many as a hundred spots may be present on each cheek in other cases and be evident also on the soft palate Koplik spots usually appear before the exanthem, often they appear before the symptoms of coryza and fever Therefore, they are frequently of value in making an early diagnosis They are also of value in the differential diagnosis, as they are pathognomonic of measles In looking for Koplik spots, good illumination is essential direct sunlight shining on the buccal surface is best a negative diagnosis of the presence of the spots cannot be made with certainty, if artificial light has been used Koplick spots histologically are collections of debris, dead epithelial cells They must be differentiated from ulceration of the mucous membrane from the teeth or other cause, from thrush, from food particles A general roughness of the mucous membrane of the mouth usually accompanies Koplik spots White spots similar to Koplik spots have been described on the mucous membrane of the vagina in measles. Koplik spots are present probably at some time in all cases of measles, but are not always seen, perhaps they were looked for too soon or too late, or with insufficient care

In most cases the appearance of the typical rash establishes the diagnosis The eruption usually may be detected two or three days before it is evident to the eye under ordinary illumination, if a mercury vapor lamp is used Similarly the lesions are evident for several days after they have faded in ordinary light. It would seem that the exanthem and the enanthem develop simultaneously, but the thickness of the skin as compared with that of the mucous membrane make the presence of the latter evident sooner

Some enlargement of the lymph glands occurs in measles the post aural glands almost invariably are enlarged, and the ability to feel them in a case of doubtful diagnosis is corroborative evidence of either measles or German measles

The changes in the white blood count are characteristic of the disease In the incubation period there is usually a leucocytosis, 15,000 to 20 000 white blood cells per cu mm with the onset of the symptoms there is a normal white blood count or a leukopenia 5 000 to 10 000 white blood cells per cu mm

A high white count during the acute phase of a coryza ordinarily will rule out measles During complications, as pneumonia, the white count may or may not be elevated

In some cases, where the diagnosis has been in doubt it may be determined subsequently by the occurrence of other cases seemingly contracted from the

patient or by the subsequent immunity of the patient to measles in spite of one or more opportunities to contract the disease

Differential Diagnosis

In the differential diagnosis of measles one must consider the acute respiratory infections as influenza or grippe other exanthemata notably rubella small pox and scarlet fever and certain skin lesions as the drug rashes toxic rashes and allergic eruptions Typhoid fever must be differentiated occasionally from measles

Certain types of grippe or influenza may simulate the preeruptive stage of measles rhinopharyngitis laryngitis cough toxicity and a low white blood count are common to the two conditions The presence of Koplik spots and history of exposure to measles helps to establish the diagnosis the prevalence of a definite epidemic of grippe and absence of one of measles or vice versa are of importance in diagnosis In hospitals any child with an acute respiratory infection should be isolated this may forestall not only an epidemic of measles but also of grippe

Small pox is characterized by a leukopenia fever headache and prostration the early pox may simulate the macules of measles but the onset is sudden respiratory symptoms are not pronounced and Koplik spots are absent.

Rubella or German measles has an exanthem very similar to measles The enanthem and the Koplik spots are absent and the patient is either afebrile or has only a small rise of temperature the lymph nodes usually are more enlarged in German measles especially the posterior cervical and post auricular nodes

Scarlet fever has a sudden onset with vomiting the throat is distinctly sore and the sneezing coryza and cough are not marked the rash is diffuse even rather than blotchy and seldom involves the face

Allergic reactions sometimes simulate measles the coryza cough eruption and febrile course may be similar There are no Koplik spots in these allergic reactions It is quite probable that many reported cases of recurrent measles were due to a protein reaction

Some drugs may lead to an eruption simulating measles especially quinine salicylates the hydantoin derivatives and sulfanilamide and allied drugs Over dosing with sulfanilamide has been noticed to produce an eruption indistinguishable from measles Phenyl ethyl hydantoin nirvanol is a drug previously used frequently in the fever treatment of chorea After the administration of this drug for 5–6 days fever coryza Koplik spots and a morbiliform eruption appear Even though the drug is continued the fever falls and the rash disappears as in measles One suspects that the toxin of measles may have some

chemical similarity to nirvanol Diphenyl hydantoin, dilantin, also may give a similar eruption and fever Thus, a child under treatment for epilepsy may develop a pseudo-measles, it is not known whether hydantoin drugs furnish any immunity to measles

Erythema multiforme and the so-called intestinal or "gut" rashes occasionally may offer difficulty in the differential diagnosis Heat rashes frequently simulate measles In general, the presence or absence of Koplik spots the pathognomonic sign of measles, is a great aid in diagnosis

Complications

The complications of measles are numerous They seem to depend on a definite diminution of resistance to bacteria as a result of the action of the contagium of the measles The complications occur for the most part during the period of defervescence or early convalescence The complications are due to secondarily invading organisms, (1) picked up during the course of the disease, or (2) present in the body for some time but showing no symptoms (patient was a carrier) or (3) present in temporarily quiescent, chronically diseased tissue, an example of the first cause would be pneumonia contracted from a patient in the next bed in a measles ward, an example of the second would be a case of diphtheria in a previously healthy carrier of the Klebs-Loeffler bacilli, and of the third would be a flare up of an otitis media a bronchiectasis or a dysentery Measles also may aggravate a previously existing pathological state as tuberculosis, diabetes, heart disease or other debility

The eyes usually escape serious complication Ulceration of the cornea occurs rarely In patients with hyperopia the ability to accommodate vision without symptoms of eye strain may be lost temporarily

Otitis media is a common complication, especially in those who have had a previous attack, a serious mastoiditis which requires operation by reason of the spread of the infection into the bone surrounding the mastoid cells may occur but is not so common as in scarlet fever The severity and nature of the otitis and mastoiditis following measles seems to depend on the type of the infecting organism Epidemics of otitis media within a measles ward occur the organisms being passed from patient to patient by the coughing

Stomatitis is a common complication of measles, especially in those whose teeth are poorly cared for It is usually ulcerative in nature and the secondary invaders are the Vincent s organisms, fusiform bacilli and spirilla The process may spread and become quite serious in poorly nourished or chronically ill individuals

Noma, or gangrenous stomatitis is a sequela of the stomatitis and greatly to be feared The first thing to be noticed is an induration and swelling in the cheek which becomes dusky red and in the course of a few hours turns black The process extends with great rapidity a bluish red zone preceding the black area It may involve both cheeks and even the lips and nostrils Hemorrhage rarely occurs and fortunately there is little or no pain, there is a very offensive odor there is not much fever but the appetite is lost the patient becomes apathetic and depressed the circulation becomes poor and death usually occurs in the course of a few days Occasionally recovery occurs with loss of considerable tissue of the cheek and jaw and with considerable deformity Noma fortunately is becoming a rare complication of measles it is not necessarily restricted to that disease

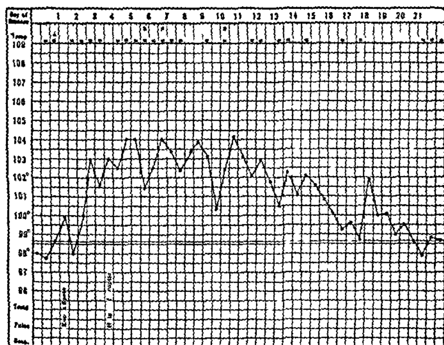


FIG 3 —Measles with mild secondary pneumonia. Child 1½ years.

There may be complications involving the tonsils and the pharynx streptococcus tonsillitis diphtheria and retropharyngeal abscesses may occur

The usual mild laryngitis of measles may be aggravated by secondary membranous or diphtheritic laryngitis, marked edema of the larynx may occur in

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enanthem of measles renders the vagina very susceptible to the gonococcus the girl who is a carrier of the gonococci usually from a previous attack of vaginitis is very likely to have a recurrence of that condition sometimes gonococcus vaginitis occurs in girls who have no history of previous attacks indicating that they were carriers When one girl in a measles ward develops vaginitis the prevention of its spread to the other girls on the ward is very difficult

A child with some chronic condition as tuberculosis heart disease nephritis enteritis diabetes or arthritis may suffer seriously from an attack of measles

The tuberculin test in a tuberculous child becomes negative during the course of measles The lowered resistance of the patient following measles may cause a flare-up of a tuberculous process miliary tuberculosis and tuberculous meningitis may follow an attack of measles

The heart muscle which was competent to take care of the circulation in spite of pericarditis or valvular defects may be unable to meet this demand during an attack of measles because of the febrile and toxic action on the myocardium decompensation may result Intercurrent attacks of rheumatic fever during measles are not so common as during scarlet fever

The diabetic child may go into coma during measles diminution in sugar tolerance occurs as the result of measles

Occasionally measles may act to relieve a functional disturbance instead of increasing it It is not uncommon for babies with impaired food tolerance to overcome that condition following an attack of measles This action probably is analogous to non specific protein therapy and to that found following typhoid fever the use of typhoid vaccine or small pox vaccination

Measles occurring in children with cyclic vomiting will initiate an attack of vomiting such children usually are very sick

Measles superimposed on some other disease usually is a cause for worry thus epidemics occurring in a children s hospital ward often accentuate the symptoms of the original disease or render the child more susceptible to complications as pneumonia Measles in a pregnant woman presents a very serious situation almost invariably the uterus empties itself puerperal sepsis is very likely to occur Every protection against contracting measles should be given to a pregnant woman who has never had the disease

Prognosis

Of the contagious diseases of childhood measles probably is most widespread It is next to diphtheria and whooping cough responsible for the largest number of fatalities the average yearly number of deaths in the United States

patients who are subject to frequent attacks of laryngitis Intubation or tracheotomy occasionally is necessary

Bronchopneumonia is the most common of the severe complications of measles It is responsible for most of the deaths from that disease The symptoms and severity of the bronchopneumonia vary greatly in different cases Thus while measles has a definite course quite constant with each patient, the bronchopneumonia is so varied in each case that it is almost individual in its symptoms The type of organism may vary with different cases The hemolytic streptococcus seems to be most virulent and disturbing of the organisms responsible for the secondary pneumonia, experimental work indicates that those who harbor hemolytic streptococci in their throats at the onset of measles are especially liable to develop pulmonary complications Bronchopneumonia frequently occurs in epidemics in a measles ward, the condition being passed from patient to patient this was noticed in the army camps during World War I and is unfortunately fairly prevalent in institutions for children There is no doubt that the pneumonia following measles is highly contagious

The onset of the pneumonia usually is detected during the defervescence of the measles The patient instead of getting better remains sick or may become more prostrated The temperature continues to stay elevated, the cough continues rales in the chest persist and difficulty in breathing and dilatation of the alæ nasi become evident The course of the pneumonia varies It may become rapidly fatal from overwhelming infection, it may spread gradually or rapidly over the whole chest and cyanosis become marked, it may be a migratory process and creep from place to place, pleurisy with empyema may occur it usually does not follow a short and sharply defined course as does a lobar pneumonia In some children the severer symptoms may subside, but the consolidation remains the temperature may fall to nearly normal, but the child continues prostrated, loses appetite and weight and dies after a few weeks It does not follow that a patient convalescing from pneumonia will develop bronchopneumonia from an attack of measles

Lymphadenitis to a marked degree is uncommon Occasionally a lymph node will suppurate

Persistent diarrhea following measles usually is due to bacillary dysentery The child, who was a carrier of the dysentery bacilli possibly from an old attack, may develop the disease as a result of the diminished resistance and the irritation of the bowel mucosa from the enanthem of the measles This complication has diminished in frequency with the diminished incidence of dysentery A patient subject to pyelitis is very likely to have a recurrence of that condition incident to an attack of measles

Gonorrheal vaginitis is a frequent complication of measles It becomes a very disturbing condition in a measles ward The vaginitis incident to the

period frequently is prolonged to from 17 to 21 days the temperature not elevated and the rash less marked By reason of the absence of local reactions at the site of injection and the fact that some lots of immune globulin have not been found very potent convalescent serum is the preferable means of obtaining passive immunity in susceptible individuals Such immunity most certainly should be given to children who are debilitated or suffering from tuberculosis or other chronic disease It should be remembered that children with attenuated measles may infect susceptible individuals with measles of usual severity

It is advisable to postpone the attack as long as possible because statistics indicate that the older the patient the less severe the disease and its complications No child should be exposed deliberately to measles so far as it is feasible the child who has been exposed should be protected by immunization with convalescent or adult serum It is especially important to protect the child under three years of age and the child with some chronic illness

In caring for a patient with measles the patient should be protected against secondary complications by preventing exposure to other infectious diseases especially the respiratory infections including colds and tonsillitis other susceptible individuals should be protected from the patient with measles

The grouping of the measles patients together is very unsatisfactory as experience in hospitals indicates that secondary complications pass from child to child Thus if at all feasible the patient with measles should be cared for at home in a room by himself and certainly in a bed by himself Only those actually caring for the child should go into the room it is advisable that physicians and nurses wear gowns and carefully wash their hands and faces before coming in contact with other people The table dishes should be boiled Secretions from the eyes nose and throat should be collected on gauze and burned Laundry should be either boiled or otherwise disinfected

Strict isolation is necessary from the onset of the symptoms until one week after the appearance of the rash After this time the patient is not contagious Respiratory secretions or pussy discharges occurring during the complications of measles do not contain the contagium of the disease After the patient is released from isolation it is advisable to open the room to the outdoors and expose the furniture bedding and other things that have come in contact with the patient to fresh air and sunlight for two or three days Fumigation of rooms is seldom practised now

Returning to school by the patient is certainly safe as far as the spread of measles is concerned two weeks after the onset of the symptoms children with uncomplicated measles usually are well enough to return by this time Of the children in the family of a measles patient those who have had measles should be able to continue at school during the illness while those who have never had the disease should not attend school for twenty days

per 100 000 population in the years 1934–1938 was from whooping cough 3 7, from diphtheria 2 5, from measles 2 4, and from scarlet fever 1 6 The ratio of deaths to the number of cases is much lower for measles than for any of the other three diseases Although the number of cases of measles in the United States shows little change, the number of deaths has diminished strikingly especially in the past 10 years that is, from 6 6 to 2 4 The reason for the lower rate probably is the diminished number of secondary complications

The prognosis in measles depends on a variety of different factors The mortality among healthy children in their homes is insignificant In institutions or army camps, where secondary epidemics are prevalent, it may be as high as o per cent The health of the individual is a factor, presence of chronic illnesses makes the disease more serious

The younger the child, the higher is the incidence of complications and the higher the death rate Children between six months and two years are the most susceptible

The time of year may play a role complications are more common in February and March than in May or June Certain epidemics show a higher mortality than others

Treatment

Prophylaxis against measles is definitely advisable but frequently difficult because exposure so often has taken place without the patient's or its parents knowledge

In prophylaxis either serum from patients convalescent from measles, as described on an earlier page in the subsection headed "Production of Passive Immunity or human immune globulin extracted from human placentas may be used The latter will be discussed in the following paragraphs

Human immune globulin extracted from human placentas has been found to give passive immunity to patients exposed to measles This immune globulin is found to give immunity also to other contagious diseases which the mothers have experienced The dose of human globulin varies with the preparation used In rare instances it is followed by local and general reactions of hypersensitiveness These reactions usually are mild and may be relieved by the subcutaneous injection of 1/2 c c of 1 1 000 solution of epinephrine As with convalescent serum injections during the first five days following exposure to measles will protect the susceptible individual If injected between the fifth and the eighth day the measles may be attenuated, as was the case with convalescent or adult serum

It has been noticed that in patients with attenuated measles the incubation

be continued for at least one week A satisfactory dose of sulfapyridine is grains 1½ (90 mgm) per pound of body weight per day for two days If the temperature has then fallen the drug may be discontinued If it still persists the drug may be continued in doses of grains 5–10 (0 3–0 6 gm) daily The dosage of sulfathiazole is the same as that of sulfapyridine

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When measles breaks out in a general hospital ward, it is advisable to quarantine the ward against the admission of patients, who have not had the disease until twenty days after the last case occurred or until no more susceptible patients are left on the ward In a hospital ward for measles patients should be separated widely and, if possible, be put in separate cubicles If pneumonia develops, the child should be removed to a separate room

In caring for the individual patient, there is no accepted specific treatment Convalescent measles serum has been tried but with indifferent success, its use in the early stages of severe measles or in children potentially open to dangerous complications would be justified

The room ordinarily should be kept moderately dark on account of the photophobia Otherwise the treatment is mainly symptomatic

The conjunctivitis and cough usually are the more disturbing symptoms, with the former cold compresses or a boric acid wash may relieve the discomfort, a sedative cough medicine, as codeine or paregoric is indicated for the latter If the extremities are cold and cyanosed and the eruption poorly marked, a hot bath often makes the eruption more pronounced improves the circulation and brings comfort to the patient Steam inhalations may be temporarily helpful for laryngitis or bronchitis Earache with reddening of the drum may be relieved by 5 per cent phenol in glycerine a few drops of which should be instilled into the canal Persistence of the otitis with bulging of the drum usually calls for paracentesis

The patient should remain in bed until symptoms are over and certainly until the temperature has been normal for three days The convalescent patient should not be allowed to overdo nor come in contact with infection

The diet of the patient during the febrile period should consist of fluids and such simple articles as cereals toast, fruit juices and milk Food should not be forced, but water should be urged Other proper foods may be given as the child gets better

The complications are treated according to general principles Measles does not contraindicate any of the usual methods of treatment For the bacterial complications of measles especially otitis media and pneumonia, the use of such drugs as sulfanilamide sulfapyridine or sulfathiazole is of definite value Otitis media usually is caused by the hemolytic streptococcus and may be treated by sulfanilamide In hemolytic streptococcic pneumonia sulfanilamide should be given while sulfapyridine or sulfathiazole should be used if the infection is pneumococcic

At the present time the recommended dose of sulfanilamide for a child would be grains 1 (60 mgm) to 1 1/2 per pound of body weight per day, also a similar amount of sodium bicarbonate should be given at the same time after the second day grains 5–10 (0 3–0 6 gm) of sulfanilamide per day should

CHAPTER XXI

SCARLET FEVER

By JAMES D TRASK AND PAUL L BOISVERT

Table of Contents

Synonyms — Scarlatina English, La scarlatine French, Scharlach German scarlatine, Italian

Definition — Scarlet fever is one result of infection with hemolytic streptococci in man and is characterized by sore throat, a diffuse rash and frequently a variety of complications and sequelae Primarily there is a local lesion and from it an erythrogenic toxin is distributed by the blood stream for a self limited period which is measured by the rash The complications rhinitis otitis, cellulitis etc are septic and represent a spread from the primary lesion The sequelae interrupt con valescence or appear in the third or fourth week and when uncomplicated depend on sterile metastatic focal lesions e g nonsuppurative adenitis nephritis arthritis, etc Any organ may be affected and all the special features of rheumatic fever of childhood have been described as sequelae of scarlet fever However the sequelae may be accompanied also by general streptococcal sepsis

Introduction

Scarlatinal toxin effective in active immunization and a potent therapeutic antitoxin are available but their use is not as well defined as for similar products in diphtheria Nevertheless the reawakened interest in streptococci and scarlet fever contributed by Dochez and Dick and Dick has endured and has corrobo rated the similar work of Moser Savchenko and Gabritschewsky of 1902 to 1907 whose methods were too crude for the practical measurement of toxin or antitoxin

Blake and Trask s clinical description of the scarlatinal toxemia and the recent bacteriological and epidemiological advances of Lancefield and of Griffith serve to correlate the work of many years and of many countries on streptococci in scarlet fever and related diseases Domagk and Fleming s great contributions to therapy have increased the importance of scarlet fever because of what they may teach about the general features of streptococcal infections some elements of which are susceptible to the new drugs

History

Many clinical features of scarlet fever and something of its epidemiology, bacteriology pathogenesis and treatment may be illustrated in a historical outline

Erysipelas was known to the ancients and therefore most likely they had scarlet fever also because streptococci from erysipelas can produce scarlet fever toxin (Coffey 1938) In 1550 Ingrassius of Palermo described the scarlatinal rash in the words totum corpus ignitum appareat The Neapolitans of his time called the disease rossaniam or rossalium A clear picture of scarlet fever and its dangerous sequelae is given in letters of 1625 and 1628 from M Doering of Breslau to his brother in law D Sennert Ruhrah (1933) translated them The

descriptions of bloody urine in post scarlatinal dropsy and stated that it contains almost always the serous and sometimes the red matter of blood Wells recognized that danger came with the advent of symptoms pointing to the head chest or abdomen

Mere sore throat as another form of scarlet fever was mentioned by Heberden (1802) Pfeufer (1819) in describing an epidemic of scarlet fever in Bamberg mentioned the occurrence of catarrhal and rheumatic afflictions which he thought were unrelated This topic was expanded by Graves (see report of 1884) and Trousseau (see report of 1869) They recognized scarlet fever without the rash and used familial outbreaks to correlate the disease with its complications and sequelae Among these Trousseau listed chorea and rheumatic heart disease

Graves and Trousseau both described the variable severity of epidemics The latter wrote when attending the clinic of Brettonneau my illustrious master taught his class that scarlatina which he had formerly heard spoken of as a very dangerous malady was then a mild affection He told us that from 1799 to 1822 he did not recollect having seen a single fatal case Bye and bye he saw it carry off many of his own patients

In an epidemic on the Island of St Bartholomew Cock (1832) recognized sore throat without a rash as scarlatinal and he described the diagnostic value of changes in papillae of the tongue Carriers took the disease to St Bartholomew and later to the Island of Montserrat Paget (1864) described surgical scarlet fever and Pospischill and Weiss (1911) wrote of the increased susceptibility of burned children to scarlet fever as demonstrated by the outbreaks of burn scarlet fever on surgical wards Goodhart (1879) observed acute dilatation of the heart in scarlatinal dropsy He had 6 cases with 5 autopsies He believed that the heart muscle was spoiled during the scarlet fever and that this might be a cause of death in post scarlatinal dropsy

The straggling nature of scarlatinal epidemics and the comparative insusceptibility of adults in a virgin soil as compared to the case in epidemics of measles was observed by Jürgensen (1896) in the Faroe Islands in 1873 and 1875 Hirsch (1883) cited three milk borne epidemics of scarlet fever from 1870 to 1875 and Power (1882) described the famous ones of St Giles St Pancras and Hendon where the cows were the source of the infection By studying return cases ' Chapin (1909) observed that scarlet fever was epidemiologically similar to diphtheria and dissimilar from measles and smallpox

Complications and sequelae were defined more carefully by Schick (1905 1907) Pospischill and Weiss (1911) Escherich and Schick (1912) and Jochmann (1914) It became clear that there were clinical similarities underlying the sequelae which might have a mechanism like serum sickness

The etiological importance of hemolytic streptococci has been mentioned in the definition and introduction and will be referred to throughout the chapter

symptoms and signs mentioned were headaches catarrhal affections of the throat, high fever, rash with petechiae and desquamation and the interruption of convalescence by a 'new storm" of symptoms which included arthritis and dropsy Two fatal cases with complications or sequelae were described, one with autopsy

Sydenham s description fifty years later, was less complete, but he added epidemiological data, and he used the name *febris scarlatina* In Swan's (1753) translation it appears that "Though the scarlet fever may happen at any time, yet it generally comes at the close of summer, when it seizes whole families but especially children ' There follows in the text a description of a mild disease characterized by fever, rash and desquamation Sydenham must have seen complications and sequelae, for he stated that sometimes a patient did badly on account of poor treatment, viz ' confining him in bed ' To-day this is held to be good treatment and getting patients up too early is considered hazardous

In his diary Cotton Mather (ed 1911) mentioned scarlet fever in New England in 1702 and his children were sick with it in 1704 Beginning in 1733 in Kingston, New Hampshire there was a severe epidemic of the throat distemper ' which spread through New England for five years Some writers have considered that it was scarlet fever, others think it was diphtheria Caulfield (1939) has reviewed the evidence and suggested that both diseases were present, diphtheria in the outlying districts and scarlet fever in Boston, whence came the material for William Douglass s description of scarlet fever which Weaver (1921) called "the first adequate description of scarlet fever in English '

These experiences in New England illustrate the problem of differential diagnosis, and it may be elaborated by a quotation from Hirsch (1883), the earliest information about scarlet fever goes hand in hand with information about measles Both morbid processes were discussed in common under various designations, by the mediaeval physicians as well as by those of the earlier centuries of the modern period and as late as the 17th century after the special features of the scarlatinal process had come to be recognized, many physicians clung to the opinion that it was only a modification of measles It was not until the middle of the 18th century that a perfectly clear understanding on this point was arrived at but there was introduced into the doctrine of scarlet fever at the same time a new error which makes itself heard even at the present day One sided emphasis placed on the inflammatory process in the throat which so often occurs in scarlatina led to its being confused with angina (diphtheritis of the throat), and the papular or vesicular efflorescences that occur not infrequently in cases where the cutaneous exanthem is severe led to its being confounded with miliary fever "

Withering (1778) helped to describe the variations of the faucial lesions also, he noted that among 139 of the worst cases 33 were in adult women and all recovered but 3 lying in women died Wells (1812) referred to Plenciz's prior

Scarlet Fever Mortality Rates per 100 000 Persons Living in England and Wales since 1838

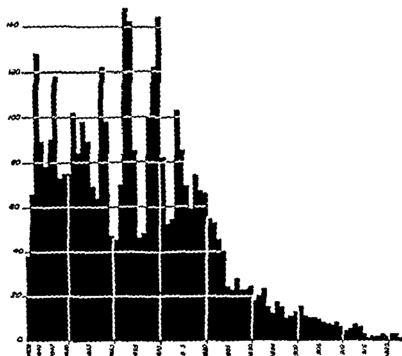


Fig 3 From Parsons (1927)

throughout the civilized world and there are seasonal variations in prevalence the disease being most frequent in winter and spring months in this country (Fig 2) and in the fall in England and Wales Recently the peak in England and Wales has come later in the year (Woods 1933) Hirsch stated that epidemics occur with about the same frequency in all seasons of the year

Scarlet fever in families presents noteworthy features First there is a tendency for the same general type of disease to occur in several children (Figs 22 and 26) and there are some famous instances where all the children in a family died in one outbreak Secondly the parents may develop scarlatinal angina without the rash *scarlatina sine eruptione* Also one child may have scarlet fever and another may have hemorrhagic nephritis cervical adenitis or rheumatic manifestations In other words these are scarlatinal equivalents They can be seen during epidemics in boarding school and have been studied with profit in England

For the completeness of the historical outline some of the workers who have helped to define the relationship of streptococci to scarlet fever are listed here, Loeffler (1884), Crooke (1885), Klein (1885), Gerge (1893), Class (1899), Baginsky and Sommerfeld (1900), Moser (1902), Brunner (1905), Savchenko (1905), Jochmann (1905), Gabritschewsky (1906, 1907), Dick and Dick (1924–1938), Dochez (1919–1924), Blake and Trask (1924–1933), Lancefield (1910–1935) Wadsworth (1929), Kirkbride and Wheeler (1926), Griffith (1926–1935), Clover (1930) Coburn and Pauli (1935) Coffey (1938), Schwentker (1943) and Hamburger (1944) Most of these individuals favored the idea that streptococci are an essential element in scarlet fever, some of them were against this view and some collected data on the problem as a by product of other studies, all made important contributions

Epidemiology

Hirsch (1883) illustrated the epidemiology of scarlet fever by comparing it with smallpox and measles He stated that the area of diffusion over the world was relatively small with scarlet fever and that it occurred as an epidemic more rarely than measles In many communities there might be ten or twenty years or more between successive scarlatinal epidemics but when they developed, the disease continued not infrequently for several years in one degree or another and often became diffused over wide stretches of country Hirsch further pointed out that sporadic cases of scarlet fever in large numbers or small were common, whereas measles occurred almost solely as an epidemic and the isolated case of measles was either the forerunner or scattered offshoot of an epidemic

A conspicuous feature of scarlet fever is the variation in mortality, which in some epidemics is almost nil and in others 30 per cent or more At present this is not such a striking feature because measles and smallpox have furnished mild epidemics in recent years However, the course of the mortality of scarlet fever over a number of years has been remarkable and is illustrated in Fig 1, which portrays data from England and Wales, where the mere incidence has remained fairly constant A similar situation holds in the United States, as for example in the State of Connecticut where the death rate has fallen gradually year after year from 5 per cent in 1895 to 0 4 per cent in 1946 (Osborn 1946) There is no sharp drop to mark the advent of therapy with antitoxin, sulfonamides and penicillin Caulfield s detailed review of early records indicates that the mortality rate was low in the 18th century The prevailing mildness of scarlet fever may represent only a phase

It is believed that scarlet fever is conspicuously mild in the tropics, although Hirsch stated that in whatever tropical regions it is met with, just as in temperate latitudes it has prevailed at one time mildly and at another time in a disastrous form Scarlet fever is endemic in thickly populated districts in the temperate zone

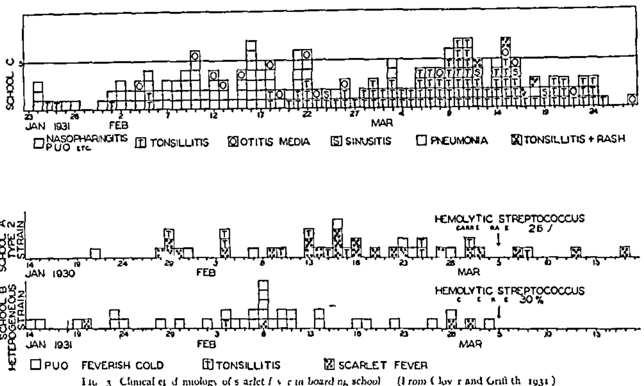


Fig 3 Clinical epidemiology of scarlet fever in boarding school (From Glover and Griffith 1931)

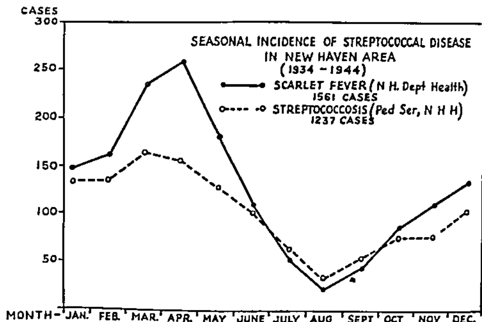


Fig 2 Seasonal incidence of scarlet fever as reported to New Haven Department of Health and of streptococcosis as occurring on the pediatric service of New Haven Hospital 1934 to 1944

by Glover and Griffith (1931) Figs 3 and 4 are taken from their paper and some of their conclusions are quoted in the following paragraphs

(2) Infection of the throat with hemolytic streptococci produces varying clinical pictures in different persons These include first a symptomless infection or healthy carrier state secondly tonsillitis, thirdly, febricula, feverish catarrh, or pharyngitis without noticeable sore throat fourthly scarlet fever Any of the latter three conditions may be followed by otitis media or by acute rheumatism

(6) In any epidemic of scarlet fever cases of tonsillitis and mild pharyngitis occur side by side with cases of scarlet fever and, if bacteriological examinations are made numbers of healthy carriers will also be detected, all yielding the same type of hemolytic streptococcus as the scarlatinal cases

(8) Epidemics of measles and influenza even in good hygienic conditions increase the spread of hemolytic streptococci, which are the chief cause of serious complications in these diseases

(9) Often, however epidemics of tonsillitis and high carrier rates of hemolytic streptococci are signs of the existence of environmental conditions which favor a rapid and easy transmission of infection Chief of such conditions are the following — too great proximity of beds deficient floor areas and deficient ventilation in dormitories'

Clinical bacteriological studies such as the above have been made infrequently here, one by Zuger (1935) and the recent study by Boisvert and Bearg (1942) of 50 scarlatinal families and of an epidemic of scarlet fever in a kindergarten confirmed the wide distribution of hemolytic streptococci in the exposed population and the common occurrence of a variety of clinical manifestations of streptococcal infection including rheumatic fever (Figs 5, 6 Table I)

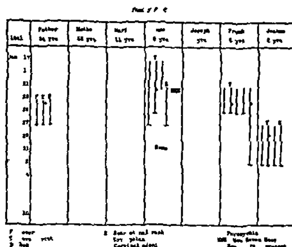


Fig 5 Note variety of clinical types of streptococcal disease in large family including streptococcal pharyngitis, erysipelas cervical adenitis and scarlet fever A healthy carrier is shown also *Hemolytic streptococci were group A type 1 organisms* This type was common in New Haven during the winter 1940–1941

Etiology

Susceptibility

Susceptibility to scarlet fever is limited to man, but infection with scarlatinal streptococci has been observed in mastitis in cows (Klein 1885 1887) and in erysipelas in rhesus monkeys (Boisvert, 1940) Scarlet fever has been produced experimentally in the chimpanzee but it could not be done regularly (Landsteiner Levaditi and Prasek 1911)

In a population previously free of the disease a high degree of susceptibility to measles exists at all ages but in scarlet fever the attack rate is low after 15 years of age regardless of the apparent lack of prior infection (Fig 7)

Donnally (1916) found that half of the cases of scarlet fever occur in children between 3 and 8 years and about 90 per cent occur in those under 15 years of age

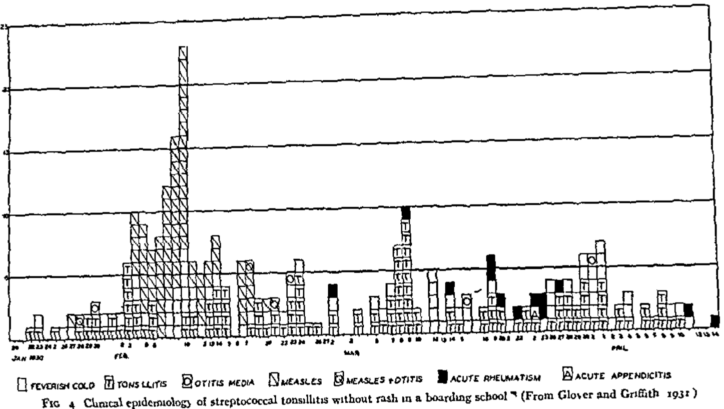


FIG 4 Clinical epidemiology of streptococcal tonsillitis without rash in a boarding school (From Glover and Griffith 1931)

TABLE I

VARIETY OF HEMOLYTIC STREPTOCOCCI IN CHILDREN'S THROATS AND RELATIONSHIP TO DISEASE AND INFECTIOUSNESS

Kindergarten Children	Hemolytic Streptococci in Throat		Streptococcal Disease	
	Group	Type	In Child	Carried to Family
R C	A	3	+	+
N T	A	3	+	+
P D	A	3	+	+
B R	A	3	+	+
M R	A	3	+	+
A. P	A	3	+	
J M	A	3	+	
M B	A	3	+	
P S	A	3	+	
B F	A	3	+	
B G	A	3	+	
C P	A	3	+	
C T	A	3	+	
E M	A	3		+
G S	A	3		+
A S	A	3		+
N S	A			
G F	A			
W M	B			
J S	C			
D K	G			
D S	C			
J H	G			

dilution of 1 to 1 000 or 1 to 5 000 is necessary to have a skin test dose of toxin in 0 1 c c volume The dilution eliminates sufficient non specific factors to make the test practical

Theoretically the Dick test measures the amount of scarlatinal antitoxin in the blood If multiples of the skin test dose were used a greater proportion of positive reactions should be found and it should be possible to place individuals into groups with reference to the amount of toxin necessary to cause a positive skin test Henry and Lewis (1925) found that this was the case and that the *amount of antitoxin in the blood varied with the grouping Their units are trans*posed into skin test doses and are expressed in Table II

Scarlet fever is reported uncommonly now in the tropics but the incidence of negative Dick tests there is as high or higher than elsewhere Plummer (1938)

In the absence of a prior attack, about 2 children out of 3 between 3 and 8 years of age contracted scarlet fever, if exposed at home Sex is not a factor of importance in young children In older children and in adults the disease is slightly more common in females Pospischill and Weiss (1911) observed that in hospital practice children with burns were unusually susceptible

FIG 6 Note scarlet fever in 9 and 7 year-old children and streptococcal pharyngitis without rash in mother and two older children Father had negative nose and throat cultures and remained well Group A type 1 hemolytic streptococci recovered from sick members

Susceptibility to the scarlatinal rash can be measured by the simple and practical Dick test (Dick and Dick, 1924 a) It consists in the intracutaneous injection of a high dilution of scarlatinal toxin obtained in sterile filtrates of culture of streptococcus scarlatinae Dick and Dick (1938) state that the tests should be read in 18 to 24 hours if read too early true negatives may appear positive and if read too late, true positives may appear negative Any erythema of 1 cm or more in any diameter at the site of injection is considered a positive test A negative result is any smaller reaction The volume of the inoculum should be 0 1 c c The unit of toxin is called the skin test dose and was defined by Dick and Dick (1925 c) as the amount of toxin which will give a positive reaction in individuals susceptible to scarlet fever and a negative reaction in immune individuals

Substances in culture filtrates other than scarlatinal toxin will produce erythema on intracutaneous inoculation and one reason for the success of the test is that some scarlatinal streptococci produce so much toxin in broth cultures that a

TABLE II

Skin Sensitivity to Graded Doses of Toxin and Amounts of Antitoxin in Blood Serum

(From Henry and Lewis 1925)

Groups	Skin Tests					Antitoxin in Serum
	Skin Tests Doses of Toxin					Skin Test Doses of Toxin
	4	2	1	½	¼	Neutralized by 1 c c of Serum
i	–	–	–	–	–	125
ii	+	–	–	–	–	100
iii	+	+	–	–	–	
iv	+	+	+	–	–	
v	+	+	+	+	–	— (less than 25)
vi	+	+	+	+	+	— (less than 25)

two of the infants were negative also to a skin test with 50 skin test doses of toxin In this connection the rarity of scarlet fever in the first year of life is of considerable interest

Following infancy the incidence of positive reactions to the Dick test rapidly increases and remains at its peak of about 65 to 75 per cent for 3 to 4 years Thereafter positive reactions decrease in incidence as with the Schick test for diphtheria

The Dick test has been used widely and has had much to do with the general acceptance of the streptococcal etiology of scarlet fever Obviously the test is practical and useful but *it measures immunity to the rash* and *not immunity to infection with scarlatinal streptococci* For antibacterial immunity no practical test has appeared and no data have been adduced to show that antitoxic and antibacterial immunity are related essentially In the experimental scarlet fever of Dick and Dick (19 3 1924 b) among 11 volunteers 3 got scarlet fever 3 contracted streptococcal tonsillitis without a rash and 5 remained well after the swabbing of the throat with scarlatinal streptococci Theoretically it is reasonable to believe that in a Dick negative individual with a given scarlatinal infection *of the throat the lesion in the throat would have been more severe in the absence* of antitoxic immunity Without the antitoxin there would then have been a greater local reaction to the toxin and hence more devitalized tissue in which streptococci might grow It is difficult to measure the importance of this but Banks (1933) noted in the highly satisfactory intravenous treatment with antitoxin that the pharyngeal edema quickly subsided

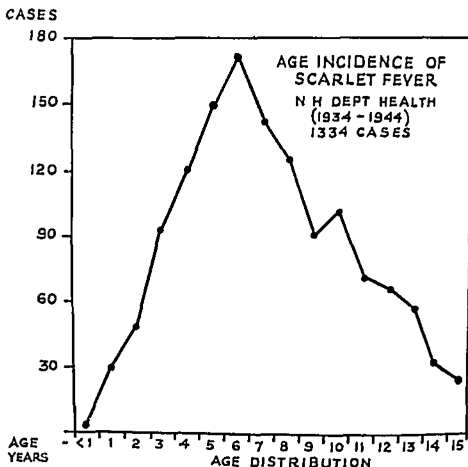


FIG 7 Age incidence of scarlet fever in 1 334 patients under 16 years of age

found greater amounts of scarlatinal antitoxin in serum from tropical zones than in comparable samples from Canada The differences began in childhood and Plummer thought that this might be significant

There are occasions when a negative Dick test may not indicate the presence of circulating antitoxin Normal laboratory animals do not have circulating anti toxin, and yet, excepting some rabbits and some goats they are singularly un susceptible to the toxin In man too this lack of susceptibility in the absence of antitoxin was demonstrated by Cooke (1927) in newborn children They had antitoxin, if their mothers were Dick negative and had none if their mothers were Dick positive but 51 infants in a series of 53 were Dick negative even though their mothers were Dick positive and had no humoral antitoxin Thirty

cation of the origin and course of the epidemics which are known to have characteristic features, (1) explosiveness (2) increased age incidence (3) relation to unpasteurized milk Increase in the age incidence was present in about 50 per cent of epidemics (Godfrey 1929) Scarlet fever without rash was common and amounted to 61 of 108 cases with Scammon and associates (1927) and to 40 per cent of cases with Stebbins and associates (1937) The latter authors compared 3 epidemics of scarlet fever and 4 of septic sore throat borne by milk or cream The 7 took place in communities of 6 000 or less in New York State Some of the data are presented in Tables III IV and V Table III shows that there were more deaths from scarlet fever than from septic sore throat The case fatality rates were 1 9 and 1 1 per cent respectively Otherwise the diseases seemed much alike in respect to age incidence and in the general similarity of complications and sequelae listed in Table IV The relative incidence of these differed

TABLE III

COMPARISON OF MILK BORNE EPIDEMICS OF SCARLET FEVER AND SEPTIC SORE THROAT

(From Stebbins Ingraham and Reed 1937)

Scarlet Fever	Cases	Deaths	Per Cent Cases Over 15 Years	Cases Per 100 Qts Milk Incriminated Dairies	Cases Per 100 Qts Milk Other Dairies
Oswego	532	8	71	145	6
Wellsville	200	6	69	27	1
Red Creek	73	2	50	43	
Septic Sore Throat					
Baldwinsville	500	7	75	107	4
Corfu	112	0		88	8
Dryden	56	1	88	62	2
Waterloo	5	0	71	51	0 3

from that customary in scarlet fever Arthritis pneumonia and erysipelas were high and nephritis was low The abnormal age distribution may have had something to do with this

In an epidemic of septic sore throat partly milk borne Winslow and Hubbard (1916) recorded the relation between age and the type of complications and sequelae Some of their data are shown in Table V In evaluating it and Table IV one realizes that in the emergency of epidemics uniformity of diagnostic criteria is not attainable but it seems likely that the positive identification of quinsy and

Dissemination

Infection by Contact, Infection of Injured Tissues, Milk Borne Epidemics — Typical scarlet fever is communicated by contact Surgical, puerperal and burn scarlet fever represent infection of injured tissues Milk borne scarlet fever is another method of infection of practical importance and of special theoretical interest because of the comparative data such epidemics afford

The usual habitat of hemolytic streptococci pathogenic for man is the human throat (Hare, 1935) They have been found in the air of hospital wards by Brown and Allison (1935) and in the dust of New York s subways (Buchbinder Solotorovsky and Solowey, 1938) Hamburger and associates (1944 1946) expanded on these studies from the standpoint of transmission of disease among military personnel In scarlet fever the streptococci are demonstrable regularly in the primary lesion and in purulent exudates from adjacent or metastatic foci (Baginsky and Sommerfeld 1900, 1902) It is not known what renders streptococci communicable in one case and not in another Crowding dosage (infected milk), predisposing infections (measles influenza) are supposed to be important adjuncts Infectiousness has been measured by recording the incidence of return cases" when individuals convalescent from scarlet fever, are discharged to their homes to mingle with their previously unaffected siblings Chapin (1909 1910) used this method to describe the laws of infectiousness and show the futility of fumigation He observed that there was but little tendency for scarlet fever to spread beyond the family group even in crowded tenements with conveniences shared by all

Arnold (1927) believed that the majority of cases cease to be infectious some time during the second fortnight of scarlet fever so that at the end of the fourth week only a small percentage remain so ' Out of this small percentage some probably remain infectious for several months, it is possible a still smaller number retain the power of infecting for a much longer period perhaps even so long as a year Gordon (1927 1932, 1934) found that the incidence of return cases was related to streptococci in nasal cultures of convalescents and also related to age and season being high when children under 15 years went home in cold months Individuals over 15 discharged in the summer and fall seldom led to secondary cases

Milk and Food

Bussey and Kober (1909) collected references to 74 milk borne epidemics of scarlet fever Epidemics due to ice cream and salad are known (Ramsey, 1925, Scammon and associates 1927) Milk borne epidemics are of special interest because the new methods of classifying streptococci permit more certain identifi

there is unity in respect to type, also The steps leading to this point of view have appeared slowly because there has been much technical difficulty in working with streptococci Moser and Pirquet (1902) used the agglutination reaction to define specific scarlatinal streptococci Schottmüller (1903) introduced the use of blood

TABLE V

COMPLICATIONS AND SEQUELAE ACCORDING TO AGE IN MILK BORNE AND CONTACT SEPTIC SORE THROAT

(From Winslow and Hubbard 1916)

Age Periods	Under 11 Yrs	11 20 Yrs	21-30 Yrs	31-40 Yrs.	41-50 Yrs	51-60 Yrs	Over 60 Yrs
Totals	226	145	181	190	100	36	18
Percentage of Above Cases Showing Each Condition							
Quinsy	1	5	16	13	9	33	0
Adenitis	63	58	51	48	44	50	14
Otitis Media	15	6	8	9	3	7	7
Rheumatism	2	7	10	21	26	0	7
Erysipelas	0	1	0	1	1	7	14
Nephritis	1	3	3	3	5	10	7
Endocarditis	1	1	1	0	0	3	0

Totals in each age group were calculated from another table in the paper

TABLE VI

MILK BORNE SCARLET FEVER ATTACK RATE REFERRED TO AGE AND MILK CONSUMPTION AMONG REGULAR CUSTOMERS OF INCRIMINATED MILK SUPPLY

(From Stebbins Ingraham and Reed 1937)

Average Daily Milk Consumption in Ounces	0-14 Yrs			Over 15 Yrs		
	Exposed	Cases	Rate %	Exposed	Cases	Rate %
None	17	2	12	90	15	17
1 to 7	29	8	28	227	57	25
8+	205	84	41	230	95	41

agar and described *S hemolyticus* and *S viridans* The next few years saw much evidence about streptococci in disease which could not be harmonized with the current views of scarlet fever and the subject rested for years There was renewed interest in the problem when Dochez Avery and Lancefield (1919) devel

erysipelas would be satisfactory Therefore, their incidence in the milk borne scarlet fever, of Table IV, is most likely related to the elevated age incidence

In milk borne scarlet fever Stebbins and associates (1937) found no relation *between age and infection (see Table VI), but they described a close relation* between age and the incidence of the scarlatinal rash, the curve for which ran parallel to and slightly above that for the age incidence of positive Dick tests in a similar population, rural New York

The infectiousness of the sick in one of the milk borne outbreaks of Stebbins and associates (1937) was about 9 per cent which was the same rate as usual for epidemics of *scarlet fever in the community In the food borne epidemic* of Scammon and associates (1927) 67 cases in one locality were followed by 5 secondary cases In Winslow s (1912) large epidemic of septic sore throat the infectiousness appeared to be nil, no secondary cases were recorded

TABLE IV

COMPARISON OF COMPLICATIONS AND SEQUELAE IN MILK BORNE SCARLET FEVER AND SEPTIC SORE THROAT

(From Stebbins Ingraham and Reed 1937)

Complications and Sequelae	Scarlet Fever		Septic Sore Throat	
	Cases	*Per Cents*	*Cases*	*Per Cents*
Arthritis and Rheumatism	59	8	69	13
Otitis Media and Mastoiditis	48	7	50	10
Quinsy	6	4	48	9
Cervical Abscess	2	3	15	3
Nephritis	11	1 5	6	1
Pneumonia	6	8	5	1
Sinusitis	24	3	4	8
Erysipelas	11	1 5	6	1
Total with Complications or Sequelae	180	25	130	25

* It is noteworthy that peritonitis did not appear in the table and was not mentioned in the text (J D T)

Bacteriology

The question of unity among streptococci in scarlet fever has been important since Klein gave the name *Streptococcus scarlatinae* to strains he recovered from the cows and from blood cultures of sick children in the milk borne epidemic of 1885 To-day it appears that there is unity by and large, in respect to *group* but not in respect to the *types* which constitute the group However, in small epidemics

by a precipitin test which identifies a type specific protein (Lancefield 1938) or by an analogous agglutination test (Griffith 1926) Strains from scarlet fever have been found among most of these types (Griffith 1934 Schwentker Janney and Gordon 1943) This seems to answer the complicated question of the specificity of scarlatinal streptococci However in familial and localized epidemics there is apt to be a single type incriminated (Smith 19 6, Glover and Griffith 1931 Boisvert and Bearg 1942)

TABLE VII

IMPORTANCE OF GROUP A HEMOLYTIC STREPTOCOCCI IN PRIMARY DISEASE
337 STRAINS FROM 248 PATIENTS MAINLY PEDIATRIC
(All belong in Mrs. Lancefield s human pathogenic group)

Disease	No of Strains	Lancefield Group						Disease	No of Strains	Lancefield Group					
		A	B	C	F	G	H			A	B	C	F	G	H
Scarlet Fever (64)	113	113						Erysipelas (1[illegible])	15	15					
Tonsillitis (71)	5	5						Cellulitis (11)	11	11					
Pneumonia (9)	23	23						Meningitis (3)	5	5					
Mastoiditis (7)	12	12						Septicemia (4)	14	14					
Otitis Media (39)	92	92						Pericarditis (1)	1	1					
Suppurative Adenitis (12)	16	16						Nephritis (4)	9	9					
Sinusitis (1)	2	2						Inf Abortion (2)	2	2					
Pyelitis (1)	2	2						(Rheum Fever) (4)	5	5					

Scarlet fever toxin sometimes called the erythrogenic toxin differs in certain respects from other common bacterial toxins It is inactivated by boiling but it withstands temperatures which destroy diphtheria and tetanus toxins The animal species which will react to it are limited In small doses it is not lethal for any small laboratory animals hence presumably it was long in being discovered Savchenko (1905) detected it by its local and general reactions on subcutaneous injection in horses It was rediscovered by Dick and Dick (1924 a) by

oped improved methods, used the agglutination and protection tests together and classified into six biological groups a large number of hemolytic streptococci from the epidemic pneumonias of the war camps Tunnicliff (1920) described a biological type for scarlet fever, as did also Dochez and Bliss (1920), Bliss (1920) and others The idea that there might be a unity among scarlatinal streptococci led Dochez (1924) to produce scarlet fever antitoxin With the renewed interest in scarlet fever different types of scarlatinal streptococci soon were described by Williams (1925) Smith (1926) Griffith (1926) and others and scarlatinal streptococci were found in other diseases Now more than 20 odd scarlatinal types of hemolytic streptococci are known (Griffith 1934, Schwentker Janney and Gordon, 1943) How these are related is best told by describing Mrs Lancefield's classification of hemolytic streptococci This confusing problem could not be solved by using one biological method Mrs Lancefield developed two, a general *grouping* by one method (1933) and a more precise *typing* by another method developed earlier (1928) The former depends on a precipitin test for a specific carbohydrate which permitted the establishment of groups These were designated by the letters A, B C, D and E Subsequently the newer groups F, G H K L M and N were added to complete the twelve groups which are now recognized Group A consists of human pathogens, while the other groups may be regarded as human saprophytes and animal pathogens It is interesting that group C includes hemolytic streptococci from strangles in horses and is the only group besides A whose members are known to elaborate a soluble erythrogenic toxin like scarlet fever toxin (Coffey 1938) It is of added interest that Gabritschewsky (1906) saw a close resemblance between strangles in horses and scarlet fever in man and thereby was led to his prophylactic vaccinations for scarlet fever in man For the important groups there are appropriate methods of separating the members into types In the human group A this is accomplished by a precipitin test, which identifies type specific proteins Group A includes the majority of streptococci pathogenic for man In large general experience a limited number of strains of groups B, C G and F have been recovered from human lesions and blood cultures However the great mass of strains pathogenic for man belong to group A (Lancefield and Hare 1935 Hare 1935 Plummer, 1935, Long and Bliss, 1938, Morales Otero and Pomales Le Bron, 1936, Coffey 1938) In hemolytic streptococcal infections the relation between disease and group A was particularly close in Boisvert's (1940) experience with more than 397 strains collected from 248 patients with scarlet fever, tonsillitis erysipelas, etc All strains proved to be group A With a present pediatric experience of over ten years and embracing thousands of strains of streptococci it can be said that exceptions to this rule are rare except in newborn infants where group B organisms have secondary importance to those of group A in septicemia (Table VII)

As mentioned above, members of group A can be separated into some 50 types

of scarlet fever but excessive vomiting and diarrhea at the onset of themselves could lead to severe consequences The principal early lesions are a general lymphoid hyperplasia and a catarrhal or purulent reaction or necrosis of the pharynx The lymphoid tissue of the cervical region is especially involved and there is swelling of axillary inguinal mesenteric and periportal nodes The solitary lymph nodes of the large intestine and Peyer s patches may be as large as in typhoid fever *The spleen often is enlarged There may be an enteritis* Crooke (1885) found extensive cellular infiltration of the gastric wall in a fulminant case dead in 26 hours

The lymph nodes are large firm and on section pale Microscopically the same type of cellular reaction appears in the lymph nodes and spleen Malpighian bodies and follicles are enlarged the lymph sinuses are dilated and contain many large endothelial cells which frequently have phagocytized lymphoid cells and red blood cells

The rash fades after death, and unless petechial or hemorrhagic usually it is not observable grossly at autopsy Microscopically the blood vessels of the corium are dilated in the epidermis and in the papillae the superficial lymphatics in the same region are dilated and there is an exudative reaction in the corium The exudate sometimes is mostly serous sometimes mostly cellular and occasionally hemorrhagic When it is well marked the leucocytes are numerous in the dilated blood vessels and many have migrated into the corium and epidermis The migrated cells consist chiefly of polynuclear and non granular leucocytes but *lymphoid cells and rare eosinophils are found among them The leucocytes are* collected around the blood and lymph vessels and in the tops of the papillae The epidermis shows but slight changes beyond swelling of the cells in the stratum lucidum occasionally elsewhere a necrotic epithelial cell is found In contrast to these degenerative changes many mitotic figures are present in the rete Malpighii

In the tongue mucous membrane of the pharynx soft palate and tonsils the pathological changes are similar to those of the skin but begin earlier and are *more marked The infiltration is greatest in and over the papillae explaining the* papillary enlargement seen during life

In many cases the heart is dilated and true myocarditis with marked round cell infiltration and degenerative changes in the heart muscle have been observed and are described in the section on sequelae (Figs 20 24 25) In the parenchymatous organs there is cloudy swelling and the changes usually seen associated with rapidly fatal febrile diseases Pearce (1899) observed focal necrosis of the liver in 4 of 23 patients dying of scarlet fever between the 2nd and 32nd day In 2 of the 4 cases there was a general streptococcal infection Brody and Smith (1936) felt that focal hepatic necrosis was the one constant histological finding in scarlet fever For an example see Fig 30

human inoculation, and they developed practical methods of measuring it and using it in neutralization tests

Chemical knowledge of scarlatinal toxin is meagre (Eaton, 1938) The toxin is insoluble in acetone and absolute alcohol and is not inactivated by these substances It is destroyed by trypsin The toxin is highly reactive in susceptible human skin which at times, may detect as little as 1/100,000 c c of a crude filtrate The toxin has been concentrated (Huntoon, 1924, Hartley, 1928, Pulvertaft, 1928), and concentration may lead to the development of a method for quantitative flocculation (Rane and Wyman, 1937) In scarlatinal filtrates there are other substances which are capable of eliciting cutaneous reactions in man, heat stable toxin (Ando, 1929) and toxin "B" (Hooker and Follensby, 1934)

The question of unity among scarlet fever toxins has been under discussion (Park and Spiegel, 1925, Kirkbride and Wheeler, 1926, 1927, Kirkbride, Wheeler and Hendry, 1928) Dick and Dick (1929) described a toxin from erysipelas streptococci and another from scarlet fever streptococci Today most observers believe with Kirkbride and Wheeler that the same strains may come from erysipelas and scarlet fever (Toyoda, Moriwaki and Futagi, 1929 Coffey, 1938) Clinical and epidemiological evidence indicate also that the host and the method of inoculation determine whether erysipelas or scarlet fever will develop Multiplicity among scarlatinal toxins has been reported by other workers, Trask and Blake (1933) Wadsworth and Coffey (1935), Coffey (1938), Wickstrom (1937) Coffey found 3 main types among the toxins from 270 strains of human hemolytic streptococci The question of the minor types was not so clear, but there appeared to be a considerable number of variants six or more of them One of the three major toxins corresponded with the heterologous scarlet fever toxin" of Trask and Blake, with toxin from Canada, with toxin from Griffith's (1935) types 14, 18 and 26 and with toxin from Puerto Rican strains Accordingly, the different toxins are widely distributed The Dochez N Y 5 antitoxin neutralized 85 per cent of all scarlatinal toxins, and the therapeutic handicap of heterogeneity was lessened when Wadsworth and Coffey (1935) found that a polyvalent antitoxin prepared with Dochez's N Y 5 strain and either one of two other strains would neutralize 95 per cent of toxins and a pool of two polyvalent antitoxins neutralized all of 185 scarlatinal toxins and was still sufficiently potent to be of practical value in treatment A multiplicity of toxins may explain some failures with antitoxin failures with the Dick test (Wickstrom, 1937), and exemplifies some of the difficulties in titrating scarlatinal products

PATHOLOGY

Death may occur on the first day or several weeks after onset, and the pathology varies accordingly Presumably in acute cases death is caused by the toxin

also in the urine and after a day s delay followed a course parallel to that just outlined for the blood Experience with other cases showed that the amount of toxin in the blood varied with the extent of the primary lesion The highest level observed was in a woman with puerperal scarlet fever with metritis and pelvic peritonitis She had 330 skin test doses of toxin per c c of blood serum (Fig 17) The usual severe case had less than 1/10 of this amount of toxin in his blood Frequently however the amount of the toxemia did not correspond to the clinical estimation of intoxication (see also Cooke 1928 b) The duration of the toxemia is measured by the rash when it fades the toxemia is over (Figs 10 and 15) Toxemia and rash may be terminated artificially with therapeutic doses of antitoxin and then in a few hours the toxin is replaced by an excess of antitoxin (Figs 32 33 34) Also the toxin in the skin may be neutralized by the intracutaneous injection of antitoxin and the rash thus may be caused to fade locally the so-called Schultz Charlton rash extinction phenomenon Fig 9

The time of development of an excess of natural antitoxin in the blood as determined by the blanching test is the 14th to 18th day (Table VIII taken from Schultz and Charlton 1918) With the same method Birkhaug (1925) observed that antitoxin appeared on the 8th to 12th days The change in response to the Dick test takes place a little earlier (Topley and Wilson 1936)

3 In the first days septic processes are measured by nasal discharge and purulent otitis media later by *angina necrotans* cervical adenitis and extension of infection to cervical facial planes (bull neck Fig 16) and floor of mouth (Ludwig s angina) It is the septic type of case which is apt to have positive blood cultures for *S hemolyticus* (Figs 10 15 and 16) In these figures it should be noted that negative blood cultures were obtained at first and that during life the bacteremia was not overwhelming Jochmann (1905) did not find any positive blood culture before the 3rd day even in fatal cases This prejudiced him against the etiological importance of streptococci

It is the septic aspects of scarlet fever which respond to sulfonamides although they may be accompanied by sequelae which are not influenced favorably by the drug

4 The sequelæ appear in the 3rd and 4th weeks (Figs 18 20 22 23 26 and 29) and are characterized by *focal metastatic non suppurative lesions* Schick (1907) described their unique time relations Fig 11 their occurrence in sibling and the general clinical similarity of their febrile course He included post scarlatinal fever recurrences and scarlatinal endocarditis among the sequelae and he believed that they had a common pathogenesis which probably was similar to that of serum sickness Schick s general notion of the pathogenesis of the phases of scarlet fever is shown in Fig 12 in comparison with a similar figure of Blake s

The streptococcal antifibrinolysin test of Tillett and Garner (1934) and the antistreptolysin test of Todd (1932) are the two employed most commonly in the

In the mucopurulent exudate in the upper respiratory passages there are many streptococci (Loeffler 1884, Crooke, 1885) With well marked septic complications necrosis of pharyngeal tissue and the lesions generally associated with hemolytic streptococcal infections are demonstrable Streptococci may be found in the cervical lymphatics and distributed throughout the body, being present in the heart s blood in large numbers The pathology is discussed further under "Complications and Sequelae" For a study of the bacteriological and pathological findings see Jochmann (1905)

Pathogenesis

Four clinical divisions of scarlet fever may be made (1) primary lesion, (2) specific erythrogenic toxemia, (3) septic complications, (4) sequelae

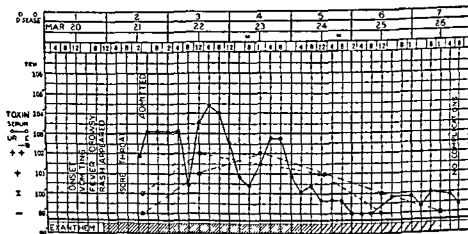


Fig 8 Study of scarlet fever toxin in blood and urine Course of specific scarlatinal toxemia in an average case without sepsis (From Trask and Blake 1924)

1 The primary lesion has been produced experimentally by Dick and Dick (1923, 1924 b 1927) and later by others by swabbing the throat of volunteers with hemolytic streptococci This still leaves a good deal to learn about the circumstances surrounding natural infection which often seems capricious

2 Savchenko (1905) having produced and detected scarlet fever toxin prepared an effective antitoxin for the specific toxemia and Gabritschewsky (1906) produced it experimentally Occasionally during active immunization with graded doses of toxin the rash and fever are produced experimentally still (Dick and Dick 1938)

The course of the specific toxemia in an average case is illustrated in Fig 8 It shows toxin in the blood on the 2nd day, reaching its highest level on the 3rd day and disappearing by the 6th day when the rash had faded largely Toxin was

also in the urine and after a day s delay followed a course parallel to that just out lined for the blood Experience with other cases showed that the amount of toxin in the blood varied with the extent of the primary lesion The highest level ob served was in a woman with puerperal scarlet fever with metritis and pelvic perit onitis She had 330 skin test doses of toxin per c c of blood serum (Fig 17) The usual severe case had less than 1/10 of this amount of toxin in his blood Frequently however the amount of the toxemia did not correspond to the clinical estimation of *intoxication (see also Cooke 1928 b) The duration of the toxemia* is measured by the rash when it fades the toxemia is over (Figs 10 and 13) Toxemia and rash may be terminated artificially with therapeutic doses of anti toxin and then in a few hours the toxin is replaced by an excess of antitoxin (Figs 32 33 34) Also the toxin in the skin may be neutralized by the intracutaneous injection of antitoxin and the rash thus may be caused to fade locally the so-called Schultz Charlton rash extinction phenomenon Fig 9

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TABLE VIII

APPEARANCE OF THE REACTING PRINCIPLE IN SERUM TAKEN ON FOLLOWING DAYS OF DISEASE

(From Schultz and Charlton 1918)

Day Taken	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Reaction	−	−	−	−	−	−	−	−	−	−	−	−	−	±	±	±	±	±	+	+	+	+
Cases Studied	2	1	3	1	1	1	2	2	2	1	1	2	1	1+ 2	1+ 2−	1+ 1−	2+ 1−	2+ 1−	2	1	[illegible]	

diagnosis of streptococcal infections These have value in atypical examples of scarlet fever where pathogenic hemolytic streptococci cannot be recovered by culture They also prove that strep-

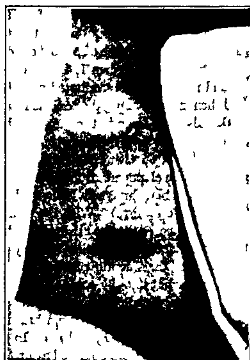


FIG 9 Schultz Charlton Phenomenon Scarlet fever rash blanched with Dochez s scarlatinal antitoxin early rash potent antitoxin strongly positive test (From Blake Trask and Lynch 1924)

tococcal infections can exist in such a mild form as to be overlooked The appearance of antifibrinolysin in the blood of a patient during the course of scarlet fever is shown in Fig 13 The trend of repeated antistreptolysin tests is similar Tests for the presence of other antibodies such as agglutinins and precipitins have not yet come into general use The diagnosis of scarlet fever usually can be made from its classical signs and symptoms alone so that in practice these tests are primarily corroborative rather than essential

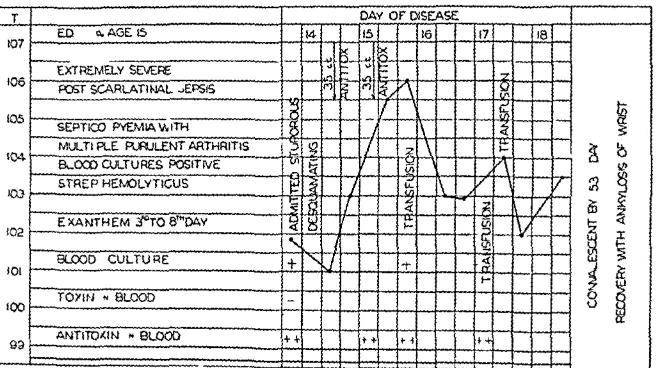


FIG 10 E D Post-scarlatinal sepsis Spontaneous disappearance of scarlet fever toxin from blood before hospitalization and natural formation of excess antitoxin Use of therapeutic antitoxin without observable effect

Allergy — Scarlet fever has been discussed in respect to allergy (Schick, 1970, Bristol 1926 Cooke, 1929), but a satisfactory description of the relationship still is lacking One must agree with Schick that there are many clinical features of the sequelae which also characterize serum sickness Coburn (1936) and Kellett (1936) have found a serological analogy between serum sickness and acute hemorrhagic nephritis in the diminution of complement in the blood serum Another similarity between rheumatic fever and serum sickness was detected by Coburn and Pauli (1939) by measuring circulating antigen and antibody in the incubation and active periods of disease

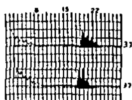
Hooker (1933) considered it unnecessary to use allergy to understand the scarlatinal rash and specific toxemia However Cooke's (1927) observation, that the skin of new born infants, even those of Dick positive mothers without scarlatinal antitoxin did not have the capacity of reacting to scarlatinal toxin has not been explained Also he (1928 b) called attention to the not uncommon disproportion between the amount of toxin in the blood in scarlet fever and the clinical severity Powers and Boisvert (1944) have emphasized the importance of age of the patient as a factor in determining the presence or absence of a scarlatinal rash It is likely that age is simply an index of infection by hemolytic streptococci and that two mechanisms in the host may be involved in the production of scarlet fever namely, sensitivity to scarlatinal toxin and absence of antitoxin In other words infants and adults may fail to develop a rash for different reasons The former have not been sensitized to scarlatinal toxin, while the latter have antitoxin in their blood

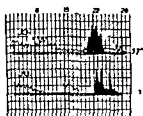
Moreover there are products from scarlatinal streptococci beside the toxin to which increased cutaneous reactivity sometimes is demonstrable This may be shown in the following situations during the course of scarlet fever, with increasing age and following inoculations with streptococcal 'nucleo-protein' The active substances consist in a vaccine of scarlatinal streptococci, Brokman (1928) and the so-called heat labile toxin of Ando (1929) which is a 'nucleo-protein from scarlatinal streptococci (Ando and Ozaki, 1930) Coburn (1931) and others have described skin tests with streptococcal products and while the reactions may be striking their basic rules and clinical application are not yet sufficiently understood to give a satisfactory definition of allergy in scarlet fever

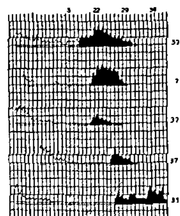
Symptomatology

Incubation

The incubation period is short usually two to six days For many years Ker (1929) used a quarantine period of one week on his wards He found this practice safe and believed that five days was the upper limit of the incubation period It







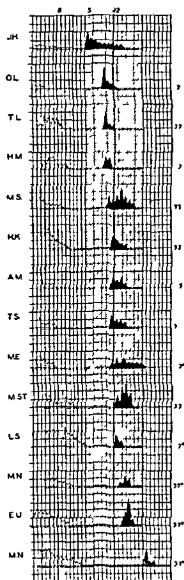
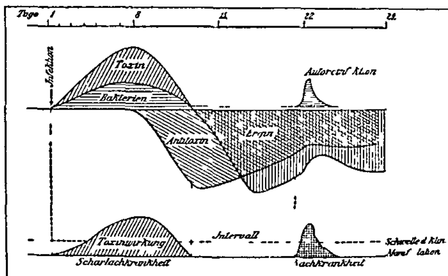


FIG 11 Schick's (1907) graphic presentation of the general similarity of various scarlatinal sequelae

was 34 to 54 hours in the experimental scarlet fever produced by Dick and Dick (1923 1924), and in the accidental infection reported by Krumwiede and associates (1914) it was two days Usually the period is symptomless, but it may be accompanied by malaise and irritation of throat and nose



Pathogenese der Nachkrankheiten des Scharlachs nach der Theorie von Schick (Nach v Pirquet Allergie Ergebnisse der Inneren Medizin und Kinderheilkunde Verlag Springer 1910 Band V)

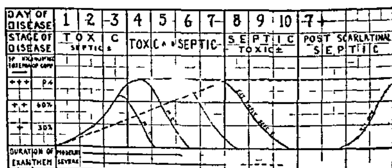


Diagram illustrating the presence of toxin in the blood during the specific toxemic phase of scarlet fever in mild to extremely severe cases the increasing incidence and importance of septic complications as the disease progresses and the appearance of antitoxin in the blood following the disappearance of toxin and the fading of the rash even though the septic phase continues

FIG 12 Schema of the pathogenesis of scarlet fever Note that Schick s hypothetical curve (shown in upper cut) for the toxin is close to one constructed by Blake and Trask (1925 a 1926) on observed values (shown in lower cut)

Symptoms

The severity, clinical manifestations, complications and sequelae are extremely variable. The disease may be so mild as to cause no indisposition and even may remain undetected until complications or sequelae develop. On the other hand it may be so severe as to cause death in a few hours. Either the toxic or septic features may predominate and either may exist with any degree of severity. Several clinical types are recognized: (1) mild, Fig. 14; (2) average, Fig. 8; (3)

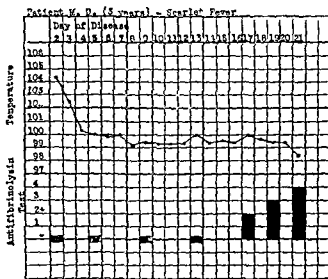


FIG. 13. Antifibrinolysin tests during scarlet fever. Child admitted with classical signs of scarlet fever of moderate severity. Throat culture showed a predominance of hemolytic streptococci. Temperature dropped rapidly toward normal; recovery was uneventful and desquamation occurred. Antifibrinolysin tests, tests were negative throughout the active stage of the disease and became increasingly positive during convalescence (Boisvert, 1940).

severe: (a) toxic, (b) septic, Fig. 10, (c) mixed, Figs. 32, 33 and 34; (4) burn scarlet fever, puerperal scarlet fever, Fig. 17, surgical scarlet fever; (5) scarlet fever without rash.

Average Case

Onset. — The onset usually is abrupt with a characteristic triad of symptoms: fever, sore throat and vomiting. It may be impossible to fix the first day of scarlet fever when it occurs during an upper respiratory infection such as influenza. In young children there may be an initial febrile convulsion but this is not com-

mon, chills or chilly sensations occur in older children or adults The primary infection usually is on the tonsils, it may be in the rhinopharynx or in the para nasal sinuses Sore throat was noted as present in 77 per cent of McCrae's (1911) series and as definitely absent in 3 per cent In the remaining 20 per cent there was no record of this symptom, presumably it was slight The fever increases rapidly to reach 103° to 105° F in a few hours Headache, anorexia and malaise are usual In addition often there is considerable anxiety restlessness and even delirium Psychic disturbances similar to alcoholic intoxication are common and are a special feature of streptococcal toxemias The pulse is unduly rapid Vomit ing was recorded in 80 per cent of McCollom s 5 000 cases In McCrae's 850 cases vomiting was present in 61 per cent

Signs — The tonsils are enlarged and bright red Frequently there are dis crete patches of white or yellowish exudate on their surface and not uncommonly there is a mucopurulent membrane which generally is confined to the tonsils and is grayish white or light yellow in color The enanthem consists of a striking erythema which spreads out diffusely from the reddened tonsils over the fauces uvula and most of the soft palate Often there are discrete red maculae and petechiae on the soft palate In well marked cases there is diffuse redness of the entire buccal mucosa Frequently there is considerable mucopus emerging from the rhinopharynx The tongue has a more or less marked gray white coat and at the tip there may be a few reddened papillae The cervical lymph nodes at the angles of the jaw are enlarged and generally tender The face is flushed, most markedly over the cheeks There is pallor about the mouth In many cases especially in those with purulent rhinitis the conjunctivae are injected as if participating in the rash Jochmann wrote of an odor like that of the lion house at the zoo as characteristic of early scarlet fever Most authors do not describe this

After the onset has been established, the *rash* usually appears on the second day McCollom says the characteristic eruption commences as a rule on the chest It may appear two or three hours after the vomiting or may be deferred from twelve to fourteen hours In rare instances the eruption does not appear for twenty four hours ' McCrae in 685 cases found the rash began on the first day in 27 per cent and in a few cases on the fourth, fifth and sixth days It generally appears first over the upper chest and neck and spreads to cover the entire body in the course of two days The distribution is somewhat variable but fairly characteristic It is most marked over the trunk and inner aspect of upper arms and thighs and least marked over the outer aspect of forearms and legs hands and feet On the face the early febrile flush becomes intensified, particularly over the cheeks The pallor about the mouth remains and in con trast to the flushed cheeks is quite striking and renders the so called circumoral pallor an obvious sign in young children in adults it is not so apparent Over the

forehead and ears the rash sometimes is well developed although it is stated that it is not marked on the face Over the palms and soles there is only a slight flush Occasionally the rash is well marked only in axillae and groins *The rash consists* of a diffuse erythema with many closely set points of deeper red which are the enlarged papillae The skin seems somewhat tense and slightly thickened Infrequently there is itching some patients speak of heat and tightness of the skin Trousseau noted that it may be swollen enough to prevent the making of a tight fist quite apart from scarlatinal arthritis or nephritis The rash is bright scarlet in color and is brightest in those with fair skins In dark skinned persons the rash is a deep red With the progress of the disease the color deepens and in some patients it may become red with a purplish tinge In well marked cases the rash increases in intensity for two or three days then gradually fades with the falling temperature and generally has faded completely between the sixth and ninth day leaving some yellow pigmentation of the skin One can make a fair approximation of the duration of the disease from the appearance of the rash

The ends of the fingers may be covered with small vesicles Occasionally there is an extensive miliarial eruption superimposed upon the rash Rarely it becomes pustular but this ordinarily causes no obvious destruction of the skin

The rash results from the blood borne soluble toxin acting on cutaneous vessels Hence the rash is generalized diffuse and blanches under pressure Frequently there are petechiae in the skin and in rare instances ecchymoses If one applies a tourniquet to the arm for five or ten minutes a crop of petechial hemorrhages will appear distal to the constriction This phenomenon is known as the Rumpel Leede s sign It is said to be obtainable regularly in scarlet fever and frequently also in other diseases and even in normal children An intense linear pigmentation of the skin folds in the antecubital spaces is known as Pastia s *sign* This may also be seen in the axillae and popliteal areas

The *rash extinction phenomenon* of Schultz and Charlton the so-called blanching test is carried out by injecting intracutaneously one half to one c c of scarlatinal antitoxin into patients at a site where the rash is diffuse *A positive test* consists of a local blanching of the rash In a negative test there is no blanching The blanching develops in 6 to 8 hours but it may be delayed until after 24 hours The skin appears normal for an area of 2 to 6 cm in diameter about the injection while the surrounding rash remains unchanged (Fig 9) Sometimes the blanched area can be recognized for two or three weeks in contrast with the general pigmentation remaining from the exanthem The reaction is obtained most clearly when a strong antitoxin is used and when the injection is made early in the disease while the rash still is developing In cases where the rash is fading the test can not be obtained regularly Also where the rash has been present several days and is considerably pigmented the reaction will be doubtful or negative Birkhaug (1925) obtained a positive blanching test with a strong scarlatinal antitoxin

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average cases consist in a moderate *spread of the local infection along the upper* respiratory passages the middle ear being involved frequently By the spread of these processes the disease may become severe in a few days

There is a well marked neutrophilic polynuclear leucocytosis which falls more or less rapidly with the defervescence of the fever Tileston and Locke (1905) found an eosinophilia to begin with the fading rash and to continue until late in convalescence They observed also a slight anemia in all but very mild cases The erythrocytes and hemoglobin returned to normal in several weeks

During the exanthematous stage there may be slight jaundice present It does not appear to be a serious sign The urine may contain albumin and a few casts as in other acute febrile diseases In addition there is an excess of urobilin in a large proportion of cases Schlesinger observed urobilin in the urine in 80 per cent of cases Generally he found urobilin on the 2nd or 3rd day and the course of the urobilinuria followed that of the rash (Jochmann 1914) Scarlet fever toxin may be found in the urine at times (Fig 8) Scarlatinal toxemia change in reactivity to the Dick test and time of appearance of antitoxin in the blood of scarlet fever patients have been discussed under Pathogenesis Sterile *blood cultures are the rule in the average case*

Mild Cases

Mild cases are of considerable importance for they again prove that streptococcal pharyngitis can be almost incredibly mild and practically asymptomatic in some people The diagnosis may not be considered until the appearance of desquamation nephritis or other complication or until the development of some secondary cases of scarlet fever The onset often is without vomiting the sore throat usually is mild and the fever often slight The rash often is poorly developed present perhaps only in the axillae and groins it may disappear in twenty four hours The tonsils may not be enlarged Generally there is a well marked erythema of the fauces and soft palate this may be the most evident sign The tongue is slightly coated and the papillae at the tip and anterior margins show either erythema or enlargement or both But the series of changes in the tongue so characteristic of scarlet fever may not occur Malaise may be so slight that the patient does not consider himself sick merely being puzzled to account for the rash *The course of the disease is short and mild Fever of a degree or two* may persist for only a day rarely for more than 3 days The rash although sometimes evanescent generally persists 1 to 2 days longer than the fever Fig 14 Septic complications usually are not present Desquamation generally is slight over the body being just perceptible over forehead and ears at the end of the first week In the 3rd week there is apt to be a more marked desquamation about the fingers and toes occasionally of the palms Post scarlatinal nephritis and lym

(Dochez) in all of 40 cases of scarlet fever during the first sixty hours of the rash

Desquamation begins at the end of the first week It is observed then over the forehead ears cheeks and chin as a fine branny scaling It spreads slowly over the body and frequently is well marked over the pubic region This fine desquamation generally is completed during the second week and is in some relation to the earlier intensity of the rash Late in the second week desquamation of the palmar and plantar surfaces of hands and feet sets in It begins about the tips of the fingers and toes In the third and fourth weeks there is the classical extensive desquamation of the palms and soles

The *tongue* shows a characteristic series of changes with sufficient regularity to permit the numbering of the early days On the first day there is a heavy white or gray white coat On the second day at the tip and anterior margins the papillae begin to show as small red spots These become more prominent on the third day They may be present as definite elevations or as small red dots about 1 millimeter in diameter McCollom (1907) noted the presence of reddened or enlarged papillae at the tip and margins of the tongue in each one of a series of 1 000 cases of scarlet fever After the third day the coat begins to desquamate, and the papillae over the dorsum of the tongue become more prominent This is the so-called strawberry tongue Desquamation of the tongue is completed by the fifth to the seventh day leaving the surface beefy red and smooth The smooth red surface is set with large papillae This is the so-called raspberry tongue which persists into the second week when it reepithelializes and returns to normal This series of changes is frequent and may be an aid in diagnosis Where there has been much mouth breathing the tongue often is smooth as if varnished, or dry and leathery

The lymph nodes at the angles of the jaws are slightly to moderately enlarged and tender The tenderness begins to disappear as the fever declines Less regularly there is some painless enlargement of postcervical, axillary, inguinal and epitrochlear nodes Occasionally the spleen is palpable

The temperature in the average case rises abruptly to 103° or 104° F or even higher and is apt to increase slightly with the appearance of the rash remaining elevated with slight remissions until the rash begins to fade and then falling by lysis to reach normal by the fifth to twelfth day (Fig 8) Rarely the fever falls by crisis The return to normal depends to a large extent on the course of the septic processes and a fever continued after the rash generally is associated with a purulent rhinopharyngitis sinusitis or otitis media

A rapid pulse is usual With a temperature of 103° F pulse rates between 130 and 160 are common Respirations ordinarily are only slightly accelerated

Cases of average severity may be further classified as to whether the toxic or septic factors predominate The toxic features are the vomiting rapid pulse prostration and psychic disturbances The septic processes associated with

phadenitis are seen occasionally in the third week Other sequel or complications also follow mild cases Fig 23

Severe Types

In discussing severity *most writers refer to events which take place in the first* two weeks and classify severe cases as toxic septic or fulminant The last group comprises cases that die in the first days sometimes before the rash appears These are the so-called pure toxic cases and apparently are not seen now

Toxic Cases — In toxic cases the features which are exaggerated are the suddenness of the onset and the rapidity and intensity of development of the usual signs and symptoms Especially marked is the fever which is apt to vary between 105° and 107° F and the pulse which is apt to run between 150 and 180 or in small children it *may be uncountable The effect on the central nervous system* is striking More or less delirium is present regularly and coma may supervene quickly Sometimes the delirium may be active but generally the prostration is intense The vomiting is severe and often persistent There is apt to be diarrhea The angina is marked and though as a rule septic processes are in abeyance usually there is a purulent rhinopharyngitis The enanthem is brilliant the entire buccal mucosa being diffusely hyperemic The tongue is heavily coated and later shows the characteristic changes The cervical nodes are slightly enlarged and tender *The rash at first may be somewhat blotchy It develops* rapidly and is apt to show many petechiae and occasionally is frankly hemorrhagic In the literature dyspnea is described as being a leading symptom

The course of the disease is apt to be stormy and desperate Septic complications are likely to develop at any time and thus prolong the disease or terminate it fatally If however they do not develop the temperature and pulse return to normal with the fading of the rash and convalescence is established early in the second week

Septic Cases — The transition from the toxic to the septic types is not sharply defined Nevertheless when septic processes are marked the differences are striking and the clinical differentiation of the two groups is made readily Age is of distinct importance as a predisposing factor small children are particularly susceptible There is also a familial predisposition to septic scarlatina It is this type of the disease which has been responsible for most of the deaths and most of the extreme cases There is generally an extensive infection of the para nasal sinuses Particularly in young children a continuous discharge pours from the *anterior and posterior nares The discharge is at first serous* later it becomes purulent or sanguino-purulent The enanthem is striking The tonsils are enormously enlarged generally meet in the midline and are covered with a thick yellowish white membrane Beneath this the tonsillar surface is ulcerated

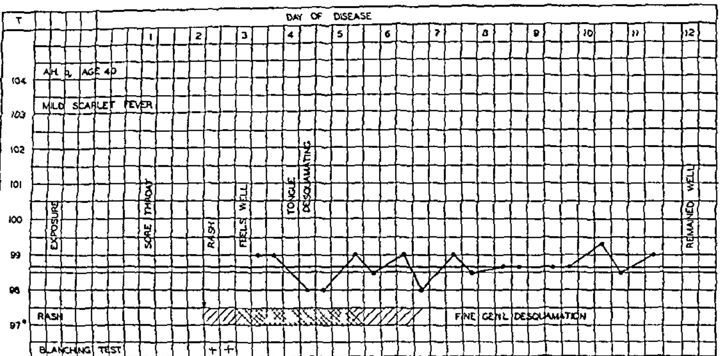


FIG 14 Mild scarlet fever Good Schultz Charlton rash extinction phenomenon so-called blanching test

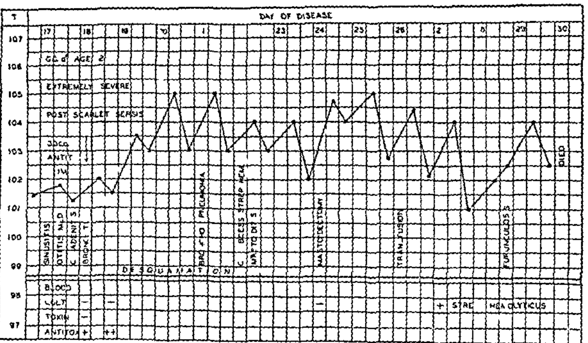


Fig. 25. C. C. Postscarlatinal sepsis. Spontaneous disappearance of scarlet fever toxin from blood before hospitalization and natural production of an excess of self made antitoxin. Use of therapeutic antitoxin was without observable effect. Fatal bronchopneumonia. Last blood culture was positive.

angina necrotans It is interesting that Loeffler (1884) and Crooke (1885) dilated upon the *necrosis* of pharyngeal tissue associated with the local presence of streptococci The rhinopharynx is full of mucopus As the disease progresses the buccal cavity may become putrid from continued mouth breathing and the extension of the septic process The tongue shows the usual scarlatinal changes and in addition is dry and leathery covered with dried mucopus Lips are parched and cracked There is marked enlargement of the cervical lymph nodes which strikingly bulge out the contour of the neck the so-called bull neck, Fig 16 There is almost always some further spread of the infection, most frequently perhaps to the middle ear Often the mastoid cells are invaded and occasionally the meninges Sometimes the meningitis is serous, there being a slight increase of polynuclear cells in a sterile spinal fluid, Fig 33 Unfortunately, there also occurs a hemolytic streptococcal meningitis Occasionally in some epidemics and frequently in others the infection progresses to the lower respiratory tract, causing a hemolytic streptococcal pneumonia (Fig 15)

The course of the septic processes is extremely variable Sometimes the tissues resist the infection well but at other times the tissues and fascial planes offer but little barrier to the spreading invasion which may lead to death relatively early Any septic process which occurs in hemolytic streptococcal infections, may develop A dreaded complication is the diffuse phlegmonous invasion of the floor of the mouth the condition known as Ludwig s angina With a rapidly spreading phlegmon there is a hard edema which may cause sufficient pressure to embarrass breathing and necessitate tracheotomy The infection may travel down the neck to produce a diffuse mediastinitis

While a leucocytosis is the rule not uncommonly in the severe cases the blood count may show little change from normal, or there may be a leucopenia (Klotz, 1904) A hemolytic streptococcemia is a common finding particularly in cases progressing to a fatal termination and as in hemolytic streptococcal sepsis in general, blood borne metastatic pyogenic foci may occur These are found in the customary sites and usually involve serous cavities Embolic phenomena are uncommon in the skin

Hemolytic streptococci are found in blood cultures in some of the severe types (Figs 10 15 and 16) In 1886–87 Klein obtained streptococci in blood cultures in 4 of 11 cases Hektoen (1903) found streptococci in the blood in 12 of 100 cases 4 of the 12 were considered mild As these studies were done before the use of pour plates was common and before the recognition of hemolytic streptococci, some of the strains may not have been scarlatinal streptococci Jochmann (1905) made blood cultures with pour plates in a series of 161 cases including many severe ones No positives were obtained before the 3rd day of disease even in fatal cases He found he could not predict on clinical grounds what cultures would be positive Except as a post mortem event he did not find great numbers

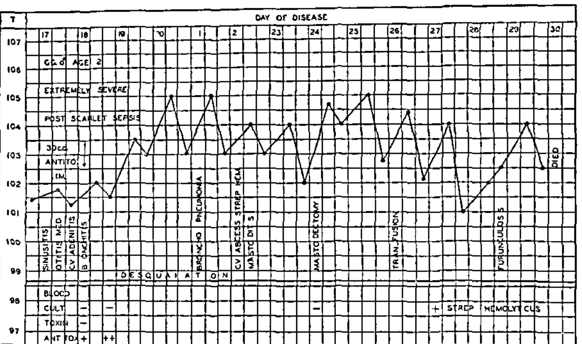


Fig 15 C C Postscarlatinal sepsis Spontaneous disappearance of scarlet fever toxin from blood before hospitalization and natural production of an excess of self made antitoxin Use of therapeutic antitoxin was without observable effect Fatal bronchopneumonia Last blood culture was positive

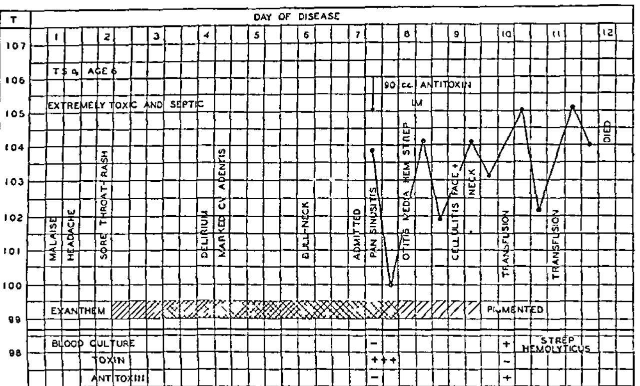


Fig 16 T S Severe toxic and septic scarlet fever Critical neutralization of specific toxemia after intramuscular injection of 90 c c of scarlatinal antitoxin but there was a progress of septic features to a fatal outcome The patient developed marked cervical adenitis so-called bull neck

of streptococci in the plates in any case Among the 25 cases that had positive cultures 24 died Nowadays finding positive cultures is not so serious a prognostic sign

In the septic and mixed types the rash usually is intense and characteristic but occasionally it may be unduly blotchy or prominent over the extremities With sepsis the primary lesion is extensive and the specific toxemia is intensified and lengthened The rash persists into the second week becomes deeply pigmented sometimes hemorrhagic and it is often difficult to decide when it has faded *A difference between the toxic and the septic types resides in the fact that* with the fading of the rash the former show marked improvement while the latter improve but slowly or not at all and pass over to the stage of post scarlatinal sepsis

After two or three weeks of irregular fever defervescence slowly sets in but it may be interrupted by a relapse of the infection with adenitis rhinitis otitis mastoiditis angina etc and then convalescence usually is not established under six weeks *Often enough some of the sequelae of scarlet fever are superimposed* On the other hand after several weeks sickness a fatal pneumonia may develop (Fig 15)

Burn Scarlet Fever Puerperal Scarlet Fever
Surgical Scarlet Fever

The usual forms of the above types are caused by hemolytic streptococci Brunner (1895) and do not differ from ordinary scarlet fever in bacteriology or specific toxemia *Special clinical features might be anticipated because the portal* of entry and the age groups may be unusual Trousseau (1869) for example spoke of arthritis as common in puerperal scarlet fever Surgical and burn scarlet fever have been mild in our clinical series but two puerperal cases died One of them had 330 skin test doses of toxin per c c. of blood serum (Fig 17) This level was six to ten times higher than common in the usual case of severe scarlet fever Trask (1926)

An atypical variety of surgical scarlet fever consists in *staphylococcal* infections with a scarlatinal rash Stevens (1927) Aranow and Wood (1942) described a *scarlatinal rash in a patient with staphylococcal osteomyelitis and bacteremia* The infecting organism produced a weak erythrogenic toxin which was neutralized by scarlatinal antitoxin This suggests that there is a quantitive rather than a qualitative difference between streptococcal and staphylococcal toxins In the five cases which we observed the rash was blotchy and atypical It lasted two or three days Three children with a subcutaneous abscess recovered but one of two with osteomyelitis died. This illustrates that such cases are uncommon but can be fatal

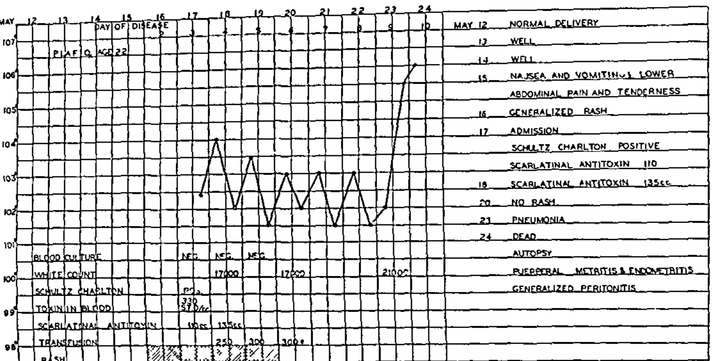


Fig 17 P L Puerperal scarlet fever Large amount of scarlet fever toxin in blood 330 skin test doses of toxin per c c There was neutralization of specific toxemia with therapeutic antitoxin but peritonitis progressed to death This patient was observed before the days of sulfonamides

Scarlet Fever without Rash

For more than a century physicians have observed that some exposed individuals especially older members of infected households *may contract sore* throat and fever but develop no rash In other respects the illness resembles scarlet fever The primary lesion in the throat appears scarlatinal and may lead to the usual complications or sequelae The disease was identified bacteriologically by Rosenow (1926) Stevens and Dochez (19 6) Nicholls (1926) and others It offers one of the obstacles in assessing attempts to stamp out scarlet fever by means of active immunization Also see Figs 3 and 4 in this connection

Relapses and Second Attacks

Immunity in infectious disease is relative not absolute and in scarlet fever relapses and second attacks are well recognized even if uncommon Ker said *that relapses occur in cases treated at home as well as in hospitals and inferred* that a new source of infection was not necessary However Gunn and Griffith (1928) observed that a new type of scarlatinal streptococcus appeared in the throat cultures in each of three cases at the onset of a relapse and persisted for some time thereafter The incidence of relapses was 0 6 per cent in McCollom s 5 000 cases about 1 per cent in Ker s 20 000 cases and 1 5 per cent among Rolles ton s 153 607 cases admitted to hospitals of the Metropolitan Asylum Board 1900–1909 In McCollom s series a second relapse was seen in 5 cases Ker s *earliest example of relapse came on the 16th day* He stated that the usual period was the 4th or 5th week He never saw a fatal relapse but from Jochmann (1914) one gathers that a relapse may be milder or more severe than the primary attack The symptoms are the same as in the primary illness sore throat fever vomiting and rash with subsequent desquamation Jochmann stated that relapses were accompanied by hematuria if this had been present in the first attack He de scribed under the term post scarlatinal angina the recurrence during the 3rd week of all the features of the primary tonsillitis without the recurrence of the rash He also used the term pseudo-relapse to describe periods of fever for 24 hours in convalescence These febrile episodes appear similar to the post scar latinal fever described by Schick (1907) Pospischill and Weiss (1911) and Escherich and Schick (1912) regarded relapses and pseudo-relapses as belonging among the second sicknesses of scarlet fever

Second attacks come many months or years after the first and are less common than relapses In his series of 5 000 cases McCollom mentioned 10 who had a prior attack Rolleston (1929) cited Kelleher s case of a woman who had 5 attacks of scarlet fever between the age of 15 and 28 years She was in Metropolitan Asylum Board hospitals for each attack There is no evidence that treat ment of the initial attack with antitoxin is a factor

Complications and Sequelae

The occurrence of complications and sequelae is characteristic of scarlet fever The common septic complications are nasal sinusitis, otitis media, suppurative adenitis and ulcerative tonsillitis The common sequel are adenitis nephritis post scarlatinal fever and arthritis Rolleston noted that the remainder of complications and sequelae occur in less than 1 per cent of all cases Presumably among the remainder he included mastoiditis lateral sinus thrombosis empyema peritonitis pyemia, endocarditis erythema nodosum erythema multiforme, purpura, gangrene of extremities, hemorrhage from large vessels, chorea and rheumatic heart disease

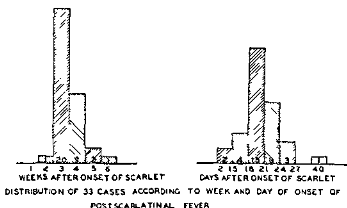
The septic complications may become prominent early in the first week and again in the period of desquamation or later They are characterized by tissue invasion and pus formation with scarlatinal streptococci in the pus The sequelae belong to the period of desquamation, characteristically they are nonsuppurative and bacteria are not demonstrable in the lesions There is, however, a relation between the complications and sequelae Often with the appearance of one or more of the sequelae there is an increase in septic activity This is evidenced by a flare up of the pharyngitis and otitic discharge suppuration of cervical lymph nodes bacteremia, etc Schick (1907) described a lymphadenitis at the angle of the jaw just preceding post scarlatinal nephritis With the onset of sequelae Pospischill noted that a swelling and increased redness in the pharynx could be observed almost invariably Jochmann corroborated this

Septic Complications

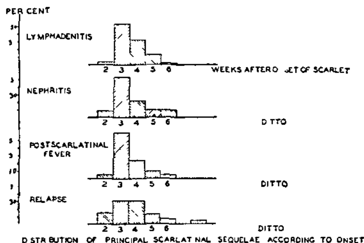
The various septic complications have been described above under "Septic Types and will be mentioned again under Treatment' Illustrative cases appear in Figs 10 15 16 17 27 28 33 34, 35 36 The complications represent a spread from the primary lesion Not uncommonly this occurs in the 3rd week and thereby raises the question of some basic similarity in the pathogenesis of the spread and of the sequelae, as was suggested above

Sequelae

The usual time of onset of sequelae is in the 3rd and 4th week (Fig 18), but post scarlatinal arthritis is apt to appear earlier i e, during the second week (Fig 23) Roughly, the period of desquamation includes the onset of all sequelae. They are related to the family background (Figs 22, 26), (Paul Salinger and Zuger 1934) to age (Fig 19 Hodges 1894), to the prevailing nature of the epidemic Illustrations of sequelae appear in Figs 11 and 18 to 30



DISTRIBUTION OF 33 CASES ACCORDING TO WEEK AND DAY OF ONSET OF POSTSCARLATINAL FEVER



D STR BUTION OF PRINCIPAL SCARLAT NAL SEQUELAE ACCORDING TO ONSET

TABLE OF SCARLAT NAL SEQUELAE

	YEARS	2	3	4	5	6	7 0	TOTAL
		WEEKS AFTER ONSET OF SCARLET						
LYMPHADENITIS	904 905	2	37	22	6	1		68
NEPHRIT S	1904 1905	2	8	7	3	3		33
POSTSCARLAT NAL FEVER	1901 1906	1	20	9	2			33
RELAPSE	190 906	1	3	6	2	1		13
TOTAL		6	78	44	13	6		147

Fig 18 Time of onset and incidence of common scarlatinal sequelæ seen by Schick (1907) among 1692 cases of scarlet fever in 1901–1906 and 627 cases in 1904–1905

Nephritis

Hematuria and edema are the usual diagnostic criteria of nephritis Ker stated It is usual in statistics to class albuminuria and true nephritis separately, but it is very difficult to draw any definite line between them It is not unusual to find tube casts in cases of slight and transient albuminuria, and the complication tends to occur at the period of convalescence at which acute nephritis with hematuria and well marked symptoms is most apt to present itself It is hard to resist the conclusion that the difference between the two conditions is only one of degree By Addis s method red blood cells may be found in the urine in children convalescing after scarlet fever and other streptococcal infections but not after pneumococcal pneumonia (Lyttle, 1933)

Generally it is considered that exposure is a predisposing factor in the production of nephritis Ker laid especial emphasis on draughts of cold air, mentioning the occurrence of 16 cases of nephritis or late albuminuria among 20 patients with scarlet fever when ventilators blew a draught of cold air on them Pospischill and Weiss and Jochmann found no prophylactic virtue in a meat free diet Nephritis may follow mild or severe cases and cases well treated with antitoxin (Fig 32) Age incidence, illustrated in Fig 19, has its peak from 5 to 9 years

The frequency and severity of nephritis has been noted to vary considerably in different epidemics Joe and Williamson (1926) found in the years 1919–22 that nephritis occurred in 1 4 to 2 7 per cent of all cases of scarlet fever admitted to the hospital but in 1923 and 1924 it occurred in 4 6 to 5 per cent In 1921–22 only 5 out of 72 deaths were due to nephritis while in 1923, 8 out of 91 deaths and in 1924 11 out of 67 deaths were due to nephritis Ker (1929) Ker found in his series of 7 608 cases of scarlet fever the incidence of nephritis was about 9 per cent In his series of 134 cases of nephritis 88 occurred between the sixteenth and twenty sixth days and 68 of these had their first symptoms between the twenty first and twenty fourth days Schick s (1907) tabulation is shown in Figs 11 and 18 Parsons (1927) suggested that post scarlatinal nephritis may have decreased in England and Wales Schick stated that the onset is apt to be preceded by a slight cervical adenitis There is some fever generally, which persists for a few days Frequently there is vomiting Puffiness of the face may be the first sign noted Sometimes hematuria is the first sign Typically the blood is observable grossly In addition the urine contains large amounts of albumin and cellular granular and hyaline casts The daily output of urine is reduced there may even be anuria All degrees of edema from slight puffiness of the face to anasarca are seen The blood pressure is elevated There is some nitrogen retention and the usual findings of acute hemorrhagic nephritis which are described in Chapter XI of Volume III of this system

Acute nephritis usually terminates in complete recovery (Aldrich 1937 Lyttle

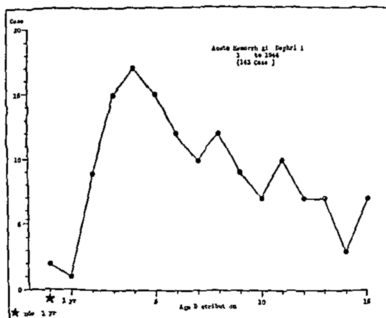


Fig 19 Post scarlatina arthritis in relation to age Weaver (1925) and acute hemorrhagic nephritis 1924 to 1944 (143 cases) Pediatric Service New Haven Hospital

and associates 1938) and post scarlatinal nephritis is no exception Death occurs in about 5 per cent of cases and chronic nephritis is rare Ker cited one case which recovered after complete suppression of urine for five days Hansborg (1925) found only 2 cases of persistent albuminuria out of 284 patients one to ten years after they were discharged from the hospital where they had been treated for post scarlatinal nephritis In one patient the albuminuria seemed to be independent of nephritis and in the other there were no symptoms of sickness other than the albuminuria However when the course is downhill death may occur in a few days Anuria increasing retention of nitrogen rising blood pressure convulsions cardiac dilatation and dyspnea are bad signs Death may seem chiefly cerebral or cardiac A pressure cone from forcing the medulla into the foramen magnum has been seen (Blackfan and McKhann 1931) Cardiac dilatation is common in acute nephritis (Rubin and Rapoport 1938) and sudden death with myocardial failure was described by Goodhart (1879) An example of scarlatinal nephritis hepatitis and myocarditis is illustrated in Figs 20 21 24 25 and 30

At autopsy the so-called scarlatinal kidneys are enlarged and the capsule strips easily leaving a surface which is mottled with red and gray spots On section

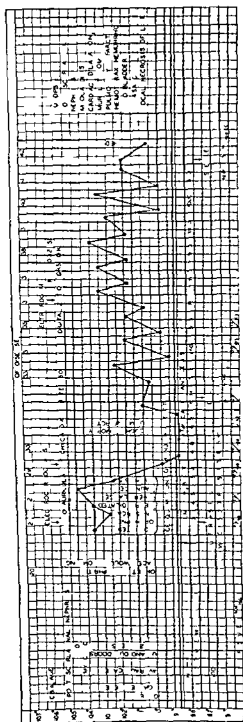


Fig 20 C B Post scarlatinal nephritis hepatitis and myocarditis Note that the blood cultures were negative and that the nitrogen retention was not excessive See Figs 17 20 21 and 26 for photograph of mural thrombi and photomicrograph of sections of heart kidney and liver

(Fig 21) the cortex is swollen, mottled, grayish and reddish gray in color The glomeruli are visible as little granules The medulla is slightly swollen and dark gray red in color Microscopically the glomeruli are large and one observes in them an increased number of nuclei indicating proliferating activity Accumulations of cells are found in Bowman s capsule and appear as crescents There may be exudation and hemorrhage also into the capsular space The epithelium of the urinary tubules undergoes degenerative changes and the tubules are largely filled with detritus desquamated cells and red blood cells There are also focal collections of round cells in the interstitial tissue Sometimes these are a prominent feature but sometimes the kidneys are negative grossly and show remarkably little microscopically (Aldrich, 1937)

Adenitis

Slight cervical adenitis involving the tonsillar nodes is common at the onset, and there is a severe adenitis seen early in the disease associated with extensive septic processes There is another type of adenitis which appears in the 3rd and 4th week and often is without obvious sepsis The disease may have been mild and convalescence otherwise uneventful Fig 22 illustrates 3 cases in the 3

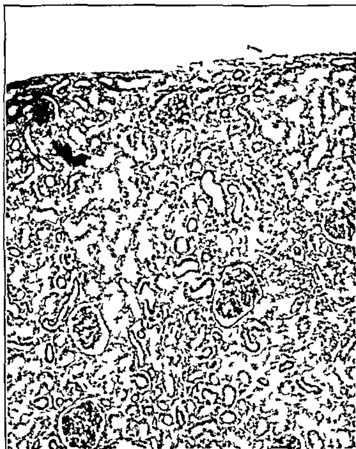


FIG 21 C B Post scarlatinal nephritis x 85 Focal accumulation of round cells increased cells in the tufts exudate in subcapsular space cellular casts in tubules and small focal hemorrhages

children of one family Ker found adenitis occurred in about 13 per cent of cases but this seems higher than common in the present mild scarlet fever Adenitis usually is accompanied by fever and sometimes is seen in conjunction with a post scarlatinal nephritis The nodes involved usually are in the cervical region but they may be in axilla or groin The enlarged nodes are about 2 to 5 cm in diameter smooth freely movable and only moderately tender The fever usually persists for a few days but the nodes remain large for many days and subside gradually or may suppurate Sometimes it takes several weeks for this to happen

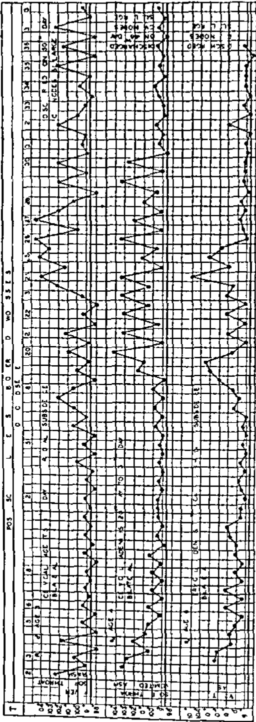


FIG 22 II Children Post scarlatinal non suppurative cervical adenitis Same type of disease in the three children of one family the primary illness was mild and was not treated with antitoxin Note that the disease lasted 5 to 7 weeks or more

Fever without Other Signs

Schick and others have observed fever without other signs to explain it This phenomenon appears in the 3rd week and is attended with little malaise or other signs of illness The fever usually is slight but may reach 103° F It lasts for a few days and sometimes recurs (Figs 11 18)

Arthritis

Ker stated Suppuration in a joint is in my experience most uncommon I cannot remember seeing more than two or three cases and they all occurred in the septic form of the disease Such a case is illustrated in Fig 10 hemolytic streptococci were cultivated from the purulent joint fluid

Another type of polyarthritis occurs more characteristically as a complication of scarlet fever and may follow mild as well as severe cases (Fig 23) This is the so-called scarlatinal rheumatism In a series of such cases Weaver (1925) obtained negative blood cultures and McClure found the joint fluid to be sterile (Ker 1929) The usual time of occurrence of scarlatinal rheumatism is during the second week It may occur earlier or later Weaver observed the complication in about 10 per cent of 2 595 cases and showed that the incidence of it increases with age (Fig 19) It is relatively uncommon in the first decade and in this respect is in contrast to scarlatinal nephritis Joe found arthritis in 4 per cent of 24 012 cases at the Edinburgh City Hospital and it was noted in 3 58 per cent of 153 607 cases in the Metropolitan Asylum Board Hospitals during 1900–1909 (Rolleston 1929) The lesion consists in a periarticular inflammation or tenosynovitis rather than a true arthritis The joints involved most commonly are those of the fingers hands wrists ankles knees and feet However any joint may be involved and there is often spasm of muscle groups Usually there is some fever (Fig 23) Rolleston described two principal forms of scarlatinal rheumatism an arthralgic form in which pains last only a few hours without any change in the appearance of the joint and a serous arthritis in which the joint is swollen and tender The muscles fasciae and tendon sheaths may be affected sometimes Usually it is stated that the arthritis is not prolonged beyond a week and that recovery is complete Generally some reservation is made for those who have had rheumatic fever previously

Some authors state that scarlatinal rheumatism may be differentiated from true rheumatic fever by the occurrence of suppuration by the failure of salicylates and by the lack of recurrences but exceptions to these criteria are common Hodges (1894) found the two conditions indistinguishable in his clinical analysis of 117 examples of post scarlatinal rheumatism and of 8 examples of post scarlatinal carditis without arthritis all collected from a series of 3 0 6 cases of scarlet

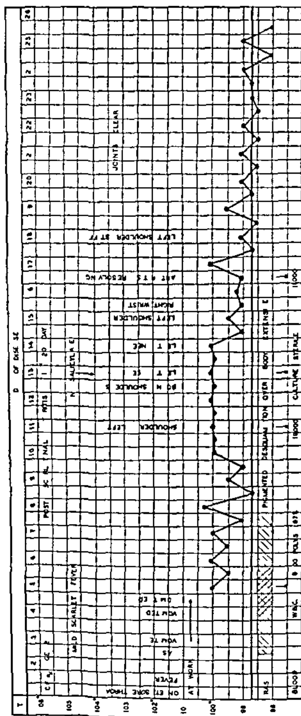


Fig 23 Post scarlatinal non suppurative arthritis Primary illness mild blood culture sterile not treated with antitoxin

fever The arthritis of rheumatic fever has different clinical manifestations according to age and in pediatric practice it is impossible to say from the immediate clinical picture that one type of acute arthritis is rheumatic and another is not Poynton (1909) followed 25 cases of scarlatinal rheumatism but no extensive series of individuals has been followed over a sufficient number of years after scarlatinal arthritis to learn the natural history of their disease Accordingly one cannot be dogmatic about the nature of scarlatinal rheumatism It seems appropriate to note that all the other features of acute rheumatic fever (chorea rheumatic heart disease rheumatic nodules pleurisy pericarditis erythema nodosum erythema multiforme purpura and hemorrhages) have been described as scarlatinal sequelae

It is stated that rheumatic fever is apt to recur when scarlet fever attacks an individual who has had rheumatic fever previously This conforms with the statement of Coburn and Pauli (1935) who observed among quiescent rheumatics that the type of sore throat which was followed by a renewal of rheumatic activity was that from which scarlatinal streptococci had been cultivated

The importance of the familial rheumatic background in the genesis of scarlatinal rheumatism and carditis was illustrated by Paul Salinger and Zuger (1934) who determined the incidence of rheumatic stigmata in four kinds of families (a) normal families (b) normal families attacked by scarlet fever (c) rheumatic families and (d) families selected because one member was known to have scarlatinal rheumatism or carditis (Table IX) The results were that the highest incidence of rheumatic stigmata 35 per cent was in Group d It is noteworthy that in families examined because of one case of scarlatinal rheumatism or carditis a large amount of preexisting rheumatic heart disease was found The data indicate that the factors which make for scarlatinal rheumatism also make for rheumatic heart disease In the pathogenesis of this condition Wilson and Schweitzer (1937) and Read Ciocco and Taussig (1938) found that heredity is an important factor and Coburn (1931) and others have implicated *Streptococcus hemolyticus* The sequelae of scarlet fever support both views

Cardiac Sequelae

In marked contrast to diphtheria serious cardiac complications are uncommon in scarlet fever and their occurrence seems more a matter of chance than in diphtheria where carditis is closely related to the severity of the pharyngeal lesion Nevertheless there are rules governing post scarlatinal carditis viz it is apt to occur in a rheumatic individual (Schick 1907) and in a member of a rheumatic family (Paul Salinger and Zuger 1934) The general question of familial predisposition in scarlet fever was mentioned by Sydenham was observed during colonial times and has become a recognized feature of the disease Formerly the

TABLE IX

THE RHEUMATIC BACKGROUND OF INDIVIDUALS WHO DEVELOP POST SCARLATINAL RHEUMATISM OR CARDITIS

(From Paul Salinger and Zuger 1934)

Type of family	Number of families	Number of individual	Per cent of those examined showing			
			I History of one or more attacks of rheumatic fever without heart disease	II History of one or more attacks of rheumatic fever with suspicious rheumatic heart disease †	III Definite rheumatic heart diseases with or without a history of rheumatic fever	Any manifestation of rheumatic fever Total of I II and III
A Control families from general and special pediatric clinics	10	9	0		4 [illegible]	4 [illegible]
B Control scarlet fever families	19	100	6 0	3 0	[illegible] 0	1 [illegible] 0
C Rheumatic fever families	4[illegible]	297	[illegible] 2	4 6	9 [illegible]	0 [illegible]
D Post scarlatinal rheumatism and carditis families	12	[illegible]	[illegible]	6 [illegible]	0 [illegible]	3[illegible] 8

This includes all members of the family who were interviewed and on whom a physical examination was performed exclusive of that member who represented the basis on which the family was chosen

† This represents the occurrence of one or more attacks of rheumatic fever in a patient who showed a systolic murmur which might under other circumstances be interpreted as a functional murmur

explanation might have been ascribed to a special type of streptococcus but Glover and Griffith (1931) found one type of scarlatinal streptococcus in large epidemics in boarding schools where there was much clinical variation in the disease Hence familial similarities in scarlet fever are more likely to depend on the host than on the parasite It may be pertinent to note here that resistance or susceptibility to infection can be bred experimentally in and out of families of mice (Webster 1937)

Cardiac Pathology —The literature indicates that true scarlatinal cardiac lesions occur and an example is illustrated in Figs 4 and 25 Stegemann (1914) described 49 scarlatinal hearts classified into three groups according to the day of the disease on which death occurred (see Table X)

TABLE X

DISTRIBUTION OF 49 SCARLATINAL HEARTS STUDIED BY STEGEMANN (1914)

Group	Number of Cases	Death on Day of Disease	Clinical – Pathological Notes
1	1	1–	12 pure toxic with catarrhal angina cervical adenitis insignificant 6 with slight necrotizing angina cervical adenitis marked General findings were cloudy swelling of the parenchymatous organs and general lymphadenopathy occasionally enteritis
2	11	5 8	All with more or less severe necrotizing angina pharyngitis and marked cervical adenitis
3	20	9– 8	All with severe septic processes some with septicopyemia 7 with nephritis

The fact that 18 of the 49 cases died before the fifth day of the disease indicates that a more severe type of scarlet fever was prevalent in Leningrad then than is common now in American cities Stegemann (Table X) attempted to correlate the pathological and clinical features of the disease In toxic cases dying early heart failure was mentioned but the physical signs were not described nor was heart failure in the late cases discussed from the clinical point of view Nothing was said of the presence or absence of diphtheria bacilli but in such a considerable series this is not a significant criticism Stegemann mentioned that the prominence of heart failure during life in the purely toxic cases was in marked contrast to the absence of gross pathological findings at autopsy In late cases frequently there was a well marked myocarditis with fatty degeneration accumulation of round cells destruction of muscle bundles and occasionally hemorrhages into the heart muscle

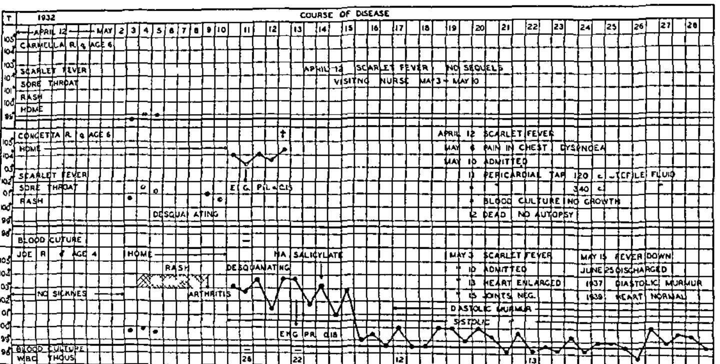


Fig 26 R Family two examples of post scarlatinal heart disease in one outbreak The twins were not identical

That these lesions are identical with true cardiac rheumatism is shown by the following considerations 1 The clinical features of such cases are those of cardiac rheumatism and as Poynton has shown their evolution is similar Post scarlatinal carditis of this type is associated with other rheumatic phenomena (polyarthritis chorea nodules etc) 3 The histological changes found in such hearts are identical with those of cardiac rheumatism Of cases of this kind examined by me one occurred in a boy of 7 who had scarlet fever and developed carditis before he left the isolation hospital He became convalescent but soon relapsed the relapse being accompanied by a crop of subcutaneous nodes The other a heart kindly sent me by Dr J B Cunson was from a girl of 15 who died of carditis developing immediately after an attack of scarlet fever In both these children the cardiac lesions were precisely those of cardiac rheumatism The inflammatory process was proliferative in type and was distributed through the endocardium pericardium and myocardium it arose in and around blood vessels and in the heart muscle it was concentrated into those highly characteristic foci the so-called *submiliary nodules*

It seems therefore that just as scarlet fever may be followed by rheumatic polyarthritis and less often by chorea so also it may lead to the establishment of a rheumatic inflammation of the heart

A basis for the difference of opinion on the occurrence of true Aschoff nodules after scarlet fever can be found in the description by Gross and Ehrlich (1934 a b) of the life history of the Aschoff nodule which does not attain its specific characteristics until after six weeks or so Relatively few die of scarlet fever at this time Moltschanow (1933) who believed in the identity of scarlatinal and rheumatic carditis could find but one instance of Aschoff nodules in the post mortem examination of 200 scarlatinal hearts The nodule illustrated in Fig 25 was collected on the 23rd day of nephritis and carditis and does not have the features of specificity

Referring to cardiac complications Ker stated These when they occur are more likely to be met with in patients suffering from arthritis but occasionally they are observed independently of this complication They are by no means common in scarlatina indeed the old teaching which put the fever almost on a par with acute rheumatism as a frequent cause of heart disease is quite unjustified Endocarditis was noted in only 0 58 per cent of 22 096 cases treated in the Metropolitan Asylum Board Hospitals and so far as my observation goes is even more rare in Edinburgh McCollom only observed it thrice in a thousand cases Soft systolic murmurs however are not infrequently present but are of little or no importance They may be accompanied by bradycardia and irregularity of the pulse and probably are due to cardiac myasthenia True endocarditis usually is febrile and the pulse tends to be rapid *Pericarditis* is even more uncommon When it occurs usually it is in a case of septic type

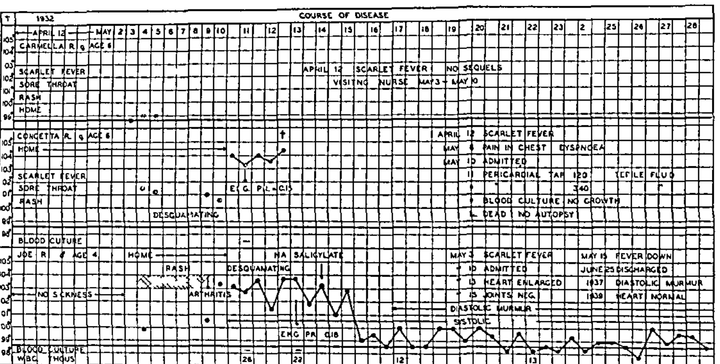


FIG 26 1 Family two examples of post scarlatinal heart disease in one outbreak The twins were not identical

cranial abscess and streptococcal meningitis Also a scarlatinal meningitis has been described which has the usual signs of meningeal irritation but with a sterile pleocytosis of the spinal fluid (Fig 33)

Rolleston (1929) wrote hemiplegia though a rare sequel is the commonest form of paralysis following scarlet fever By 1927 he had observed 4 cases in an experience of 28 years and he had collected 71 cases from the literature He added hemiplegia usually is due to cerebral embolism but may follow thrombosis hemorrhage or acute encephalitis Its prognosis is good as regards life but unfavorable as regards complete recovery apart from uremic hemiplegia which is almost invariably of short duration and leaves no sequelae

Eyes

Ordinarily no mention is made of complications or sequelae involving the eye but with streptococcal ethmoiditis periorbital edema and erythema are not uncommon An example is illustrated in Fig 27 A hemolytic streptococcal purulent conjunctivitis has been seen at the New Haven Hospital on several occasions

Skin

Besides the typical scarlatinal rash of relapses other secondary rashes occur as sequelae They consist of urticarial maculopapular papular erythematous or pityriasis like eruptions

Embolic cutaneous lesions are rare in streptococcal sepsis in children an example appears in Fig 28 This patient and a similar one did not seem dangerously sick both recovered in a few days one after sulfanilamide and the other after transfusions Post scarlatinal erythema nodosum Fig 29 and erythema multiforme are recognized

In some epidemics the incidence of herpes labialis may be high Rolleston states that it may be as high as 6 to 11 per cent Excoriations about the nares generally are mentioned in association with chronic or subacute nasal discharge Paronychiae also are described The scarlatinal streptococci for the successful experimental scarlet fever of Dick and Dick (1923) was isolated from an infected finger

Post scarlatinal purpura is uncommon Two fatal and 4 mild cases were described by Fox and Enzer (1938) who collected 50 cases from the literature The onset was during convalescence there was no thrombocytopenia and the bleeding and clotting times were not prolonged Two fatal cases of post scarlatinal purpura examined postmortem had no streptococci in the blood cultures or in the purpuric lesions

In some cases of otherwise unexplained temperature during the convalescence of scarlatina I have found slight endocarditis to be present With careful treatment the condition appears to run a favorable course, and I cannot believe that many of the patients whom I have seen affected, are likely to suffer from any subsequent cardiac trouble'

The sum of these quotations indicates that rheumatic heart disease is a rare but characteristic sequel of scarlet fever

In 2 322 cases of scarlet fever Krauss (1923) reported sudden death in 2 on the 6th and 7th days respectively At autopsy the heart was dilated and flabby, and infiltrations of round cells were present

Pericarditis — Scarlatinal pericarditis occurs as a purulent and a nonpurulent type The former usually is mentioned in discussions of septic scarlet fever In many texts nonpurulent pericarditis is spoken of as most uncommon Four examples of it were seen in about 1 200 cases of scarlet fever from the New Haven Hospital from 1923 to 1938 One apparently rheumatic died comparatively early Fig 26 Three survived and were described by Salinger and Leonard (1931), who found the condition indistinguishable from rheumatic pericarditis

Nervous System

Chorea — In current American textbooks chorea does not appear as a sequel of scarlet fever it is mentioned in this connection in the edition of 1916 of Holt's Diseases of Infancy and Childhood but not in that of 1927 by Holt and Howland Most English and continental books refer to it According to Rolleston it was noted in 15 or 06 per cent of 21 006 cases of scarlet fever admitted to the Metropolitan Asylum Board Hospitals in 1914 Parsons (1927) recorded one instance of chorea and one questionable case in the follow up at home of 500 patients discharged from the hospital after scarlet fever in Bristol England Trousseau (1869) was more enthusiastic about chorea than is usual today He stated '*St Vitus Dance* is the most important of the immediate (used here to mean remote i e immediate as the opposite of mediate) sequelae of scarlatina In children you will see this affliction following very close upon the exanthemous fever showing itself in three months two months or even in six weeks In chorea consecutive to scarlatina the bellows sound indicates the existence of cardiac lesions the result of preexisting endocarditis And sometimes, the rubbing pericardiac sound, the last characteristic manifestation, points out to us that it is by the rheumatism that the convulsive neurosis is linked with the attack of scarlatina and constitutes one of its immediate sequelae"

Other Neurological Conditions — The common neurological conditions associated with hemolytic streptococcal infections are described as scarlatinal complications and sequelae from time to time Among the most serious are intra

cranial abscess and streptococcal meningitis Also a scarlatinal meningitis has been described which has the usual signs of meningeal irritation but with a sterile pleocytosis of the spinal fluid (Fig 33)

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FIG 27 Scarlatinal ethmoiditis onset 10th day of disease Shows periorbital edema Subsequent course satisfactory Good response to sulfanilamide



FIG 28 Cutaneous embolic streptococcal lesions in child with pain in hip and positive blood culture Pink to red papules present from 5th to 10th day of disease Treated with sulfanilamide course benign recovery on 14th day Human hemolytic streptococci from skin lesions and blood culture but no further attempt was made to identify streptococci as scarlatinal

Hemorrhages

Hemorrhages from large vessels nose mouth ear or incisions are reported as sequelae from time to time Rivers (1919) described one case of bleeding from a large vessel and collected 50 cases from the literature The mortality was 90 per cent

Blood Picture

Changes in the blood picture in the period of sequelae have been described (Escherich and Schick 1912 Reznikoff 193) There may be a relative decrease *in the polymorphonuclears and considerable increase in mononuclears* The total count may be increased or decreased The eosinophilia may run an irregular course There may be splenomegaly and the diagnosis of leukemia may be discussed Post scarlatinal anemia is common

Gangrene

Post scarlatinal gangrene is another rare but dramatic sign of the vascular damage which from first to last appears to be one of the characteristic lesions of

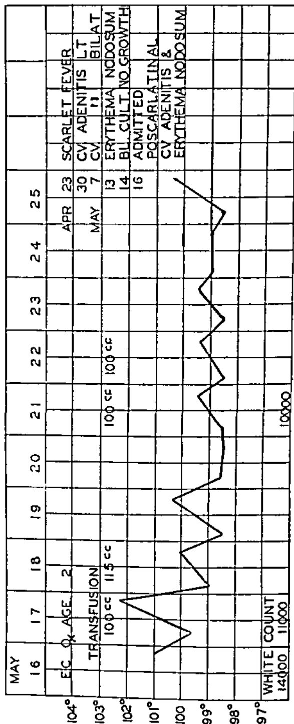


Fig 29 Post scarlatinal erythema nodosum

scarlet fever Dick Miller and Edmondson (1934) reported 1 case and found 15 referred to in the literature Some cases do surprisingly well Norton (1939) saw gangrene of both legs in 1 of 2 siblings with post scarlatinal purpura which *is another illustration of the well known familial predisposition to special types of* scarlet fever as discussed elsewhere in this chapter Our case which occurred recently resulted in recovery without amputation

Liver

In 50 autopsies on patients with scarlatinal and other streptococcal infections the one constant finding consisted in focal accumulations of round cells in the liver (Brody and Smith 1936) An example of hepatitis in a case of post scarlatinal nephritis and myocarditis is illustrated in Fig 30 An increase in urobilin in the urine appeared in 80 per cent of cases of scarlet fever according to Jochmann 1914 Rolleston stated that the frequency of jaundice ranged from 0 13 to 0 41 per cent in the Metropolitan Asylum Board Hospitals from 1903 to 1914 He found it was usually of a mild catarrhal type In our cases it occurred late in the first week and was mild In one child it was associated with considerable enlargement of liver and spleen Schottmuller (1931) described proliferative hepatitis as an uncommon but specific sequel of scarlet fever Fahr (1931) contributed the pathological findings in this condition

Respiratory System

Often measles and scarlet fever have been contrasted by noting the prominence of laryngeal and lower respiratory symptoms in measles and their infrequency in scarlet fever This has especially to do with laryngitis bronchitis bronchiolitis and pneumonia because involvement of the nasal sinus middle ear and mastoid are classical in scarlet fever

A prolonged purulent nasal discharge in a child generally is taken as a sign of *diphtheritic or scarlatinal rhinosinusitis One would expect it to be a common* source of contagion and probably it is (Hamburger and associates 1945)

Scarlatinal pneumonia is an uncommon but recognized form of scarlet fever Trask and Blake (1933) described 3 cases The course was typical of hemolytic streptococcal pneumonia Two died but one with an associated septic arthritis recovered All furnished scarlatinal streptococci which produced a different erythrogenic toxin from the most common scarlatinal type (Coffey 1938) Powers gives data on 12 children with streptococcal empyema of which 6 had scarlet fever These were treated with sulfonamides and there were no deaths Previous to chemotherapy 18 of his series of 31 (58 per cent) died

A non suppurative post scarlatinal pleurisy appearing in the period of con

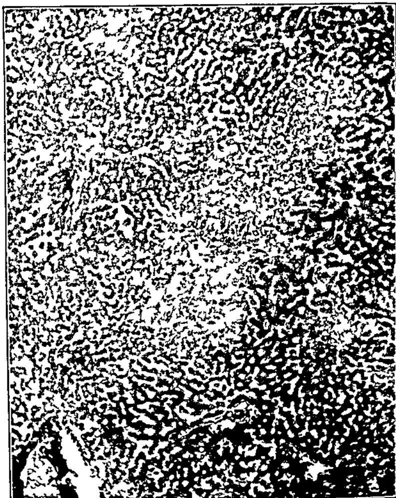


FIG 30 C B Post scarlatinal hepatitis x 90 Central necrosis hemorrhage focal accumulation of mononuclear cells

valescence is recognized The example we saw was mild and terminated in a few days

Gastrointestinal Tract

In septic scarlet fever the infectious process may extend locally to the deep tissues In the floor of the mouth this may be evidenced by Ludwig's angina, in the neck it may produce the so called bull neck (Fig 16) Retropharyngeal abscess may be another complication Gangrenous stomatitis or noma is rare Necrosis in the walls of the stomach was described by Crooke (1885) in a case

dead in 26 hours This appears too early for local suppuration and may have been a sign of cerebral injury Most likely such a fulminant case had hyperthermia Sudden fever of 107° F is sufficient to produce convulsions and cerebral lesions experimentally in kittens (Wegman 1939)

Peritonitis

Peritonitis is considered a rare complication Dunham (1921) reported one case and collected 10 others In her case peritoneal symptoms developed in the third week Hemolytic streptococci were cultivated from the peritoneal exudate obtained at laparotomy This patient recovered but two observed here subsequently did not

Persistent Slight Fever

Persistent slight fever lasting for weeks or months after scarlet fever may occur with no other sign of disease Finkelstein (1924) noted that the fever disappeared for several days or permanently following the administration of epinephrin

SCARLET FEVER AND OTHER DISEASES

Diphtheria

Among 1 029 cases of scarlet fever treated in the City Hospital 20 on admission were found to be suffering from concurrent diphtheria (Ker 1929) Among 2 595 patients with scarlet fever admitted to the Durand Hospital in 10 years 60 or 2 7 per cent were carriers of diphtheria bacilli (Weaver 19 5) With a considerable carrier rate and crowding of children one would expect post scarlatinal diphtheria to occur and it is mentioned in many texts

Appendicitis

The concurrence of appendicitis and scarlet fever may be a matter of grave concern and of much difficulty in diagnosis Weaver stated that among his patients, 4 developed acute appendicitis during scarlet fever All recovered without operation Kauffmann (1908) collected 31 cases 19 came to necropsy or to operation It would seem to be a matter of some importance that scarlet fever and acute appendicitis may co-exist Brennemann (1937) noted that some acute pharyngeal infections may have a predisposing influence for appendicitis Glover and Griffith (1931) from epidemiological evidence mentioned the same thing Rolleston stated that he had not met with appendicitis attributable to scarlet fever

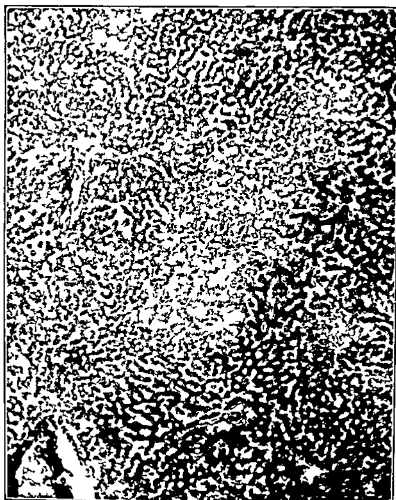


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Lobar Pneumonia

Pneumococcal lobar pneumonia may interrupt convalescence We have seen this 3 times and in each the pneumonia was mild The other acute infections are mentioned as rare concomitants of scarlet fever

Diagnosis

Scarlet fever consists of a local infection with hemolytic streptococci accompanied by signs of an erythrogenic toxemia The recognition of this may be effected by seeing the rash, inspecting the throat and mouth and by obtaining a brief consistent history

Typically the primary lesion of scarlet fever is in the throat and varies in severity from hyperemia to severe ulcerative pharyngitis, but regardless of severity the hyperemia should be diffuse and involve the soft palate Likewise the rash may have some irregularities, but as it results from a soluble toxin in the blood stream the rash should have an element of diffuseness whether it be generalized or not

Scarlet fever should be thought of in all cases of acute tonsillitis and should be considered seriously where there is vomiting at the onset considerable fever, and the tonsils are bright red with a diffuse or macular erythema on the soft palate As soon as a diffuse erythema of the skin develops perhaps limited to axillae and groins the diagnosis of scarlet fever must be made and it will in all probability, be corroborated by subsequent events

If the case is seen first after the characteristic rash has appeared, and the lingual and pharyngeal signs are present the diagnosis generally is clear If the symptoms have been unusual it may be necessary to collect serological or bacteriological data When the rash is suitable a positive blanching test will establish the diagnosis

If the case is seen after the rash has faded as late as the second week, a satisfactory history and the presence of a raspberry tongue with slight desquamation over the face or body would justify the diagnosis and finding unusual numbers of hemolytic streptococci in the nose and throat would make the diagnosis of scarlet fever practically certain

Occasionally patients are seen first with a post scarlatinal complication In some circumstances the diagnosis of scarlet fever can be made with reasonable assurance An acute hemorrhagic nephritis developing in a child, three or four weeks after an acute illness in the presence of desquamation of palms and soles would justify the diagnosis of post scarlatinal nephritis Frequently even at this period scarlatinal streptococci still may be found in nose and throat cultures

Bacteriological Serological and Epidemiological Aids to Diagnosis

Evidence of increased activity of streptococci in throat or metastatic lesions may be detected invariably in scarlet fever (Baginsky and Sommerfeld 1900 1902) Thus cultures of nose and throat on fresh rabbit s blood agar plates for hemolytic streptococci can be a great help if the medium is good Elements of good media consist in a stock prepared with an infusion of fresh (less than 24 hours dead) beef heart and peptone freed of growth inhibiting properties (neopeptone) together with the usual salts agar etc With such a basic medium blood agar plates should be prepared daily

The failure to find hemolytic streptococci is evidence against scarlet fever However the primary lesions might be in the nasal sinuses or elsewhere Taken as an isolated observation the demonstration of *Streptococcus hemolyticus* in patients does not have as much significance in the diagnosis of scarlet fever as the demonstration of *C diphtheriae* has in the diagnosis of diphtheria since the so-called normal carrier rate of group A hemolytic streptococci is about 7 per cent in a general population (Hare 1940 Powers and Boisvert 1944)

A positive Schultz Charlton blanching test (Fig 9) is proof of scarlet fever The importance of negative blanching tests is less A satisfactory negative test consists in the absence of any local blanching after using a strong antitoxin in an early diffuse rash which does not fade materially within twenty four hours of the test Such a negative test is against scarlet fever However it might indicate the presence of heterologous scarlet fever In patients sensitive to horse serum a positive test may be obscured by a local reaction to the horse serum containing the antitoxin The Dick test should be positive in the first three days and negative in convalescence If this sequence is observed it is strong evidence for scarlet fever A single test is not important A positive reaction remaining unchanged through the third week of the disease during convalescence and later is against scarlet fever if pseudo reactions and heterologous toxin can be eliminated Antifibrinolysin and antistreptolysin tests can verify the presence of hemolytic streptococcal infection including scarlet fever

Epidemiological methods are valuable diagnostic aids in households The history of scarlet fever or suggestive elements in contacts often is of considerable help Thus if one child had a running ear another desquamation and a third had hemorrhagic nephritis one could be sure that scarlet fever was nearby

Differential Diagnosis

Before the appearance of the rash scarlet fever has to be differentiated from other forms of acute tonsillitis If membrane is present diphtheria or a hema

tological dyscrasia such as infectious mononucleosis will be considered The diffuse erythema of the soft palate the proper blood count and not too much early cervical adenitis are strong points in favor of scarlet fever At this stage, especially in children occasionally one must exclude other acute infections with sudden onset Often this is impossible At times scarlet fever begins with abdominal pain and vomiting and may simulate lobar pneumonia, appendicitis or peritonitis

When *the rash is present scarlet fever must be differentiated from other in* fections in which scarlatiniform rashes develop and from rashes due to foods or drugs Unfortunately, when the diagnosis is in doubt the rash generally is too patchy or too transitory to give satisfactory blanching tests

German measles sometimes presents a rash, which cannot surely be distin *guished from that of scarlet fever, and vice versa Enlarged and slightly* tender post cervical nodes a leucopenia and the absence of hemolytic streptococci in the throat cultures would favor German measles

The occasional preliminary diffuse rash of measles chicken pox or small pox is a source of confusion In these diseases there should be leucopenia In measles *puffy eyes the catarrhal signs, the Koplik spots and in the* others the absence of the faucial signs of scarlet fever taken with the general picture should be sufficient for differentiation, but sometimes the diagnosis awaits development of the characteristic rash Again a history of exposure to known contagious disease in home or school may foster early accurate diagnosis

Septic cases of scarlet fever with a dirty membrane on the tonsils with a blotchy rash of unusual distribution and a tendency to hemorrhage justly may be confused with diphtheria The general appearance of the patient, the bacteriological findings the further development of the scarlet fever rash and the *desquamation* of the tongue should help but the two diseases may co-exist and this will cloud the diagnosis Staphylococcal osteomyelitic or other staphylococcal infections may be confused with surgical scarlet fever

Scarlet fever may be mild enough to be thought of in any trifling febrile episode and severe enough *for an acutely fatal disease*

Prognosis

The mortality has been subject to marked epidemic variations (Fig 1) Recently it has been low except in China and the Balkans

From Woods (1933) one learns that in 1851 in England and Wales deaths from scarlet fever numbered 13 634 and in 1931 the figure was 540 Thus, while the population of children *exposed to risk had increased some 40 per cent*, the deaths were less than one twenty fifth of those recorded some 80 years before Eighty years before 1851 scarlet fever, although a serious disease, was less deadly

than in 1851 and early in the 19th century it was still lightly considered At the end of the 17th century Sydenham considered scarlet fever to be a trivial illness

In other words scarlet fever has had its ups and downs in times when sanitary administration was non existent and when the domestic opportunities of infection in crowded cities were beyond anything seen in the worst slums of our generation

The diminution of deaths is due essentially to a lessened severity of the disease and no evidence has been found to prove that hospital isolation has been effective in reducing the prevalence or mortality While the absolute mortality has fallen at every age the relative importance or mortality in later life has increased in the past 30 years

In uncomplicated scarlet fever recovery is the rule in the United States Rapidly fatal cases are extremely rare now *We have seen but one of them among* more than 1 200 cases in 18 years at the New Haven Hospital This one died on the 3rd day Most deaths depend on septic complications scarlatinal nephritis or myocarditis In some epidemics a fatal pneumonia occurs Hence it follows that the prognosis depends mainly on the location of the epidemic the age of the patient the course of the septic processes and on the occurrence of sequelae These last two elements are difficult or impossible to foretell but the age family history and general condition of the patient and the type of the epidemic may be of prognostic value Many cases obviously are suffering from extreme sepsis from the start but sometimes cases that run a downhill course do not seem very sick at the onset All cases with an extensive purulent rhinopharyngitis even if apparently fairly mild are potentially severe cases

Positive blood cultures were a bad prognostic sign according to Jochmann (1907) 24 of 25 cases died Bacteremia has not been as serious as this in our experience and with sulfonamides and penicillin available old notions of prognosis must be modified considerably

Those patients who develop complications or sequelae generally are sick for a minimum of 6 weeks Of course many of these patients are sick for a longer time

PROPHYLAXIS

The usual practices of isolation have not reduced the general incidence nor can they be directly related to the reduction in mortality which sometimes preceded and sometimes followed the practice of isolation (Parsons 1927 Woods 1933) However Chapin (1913) wrote that paradoxical as it may seem there is evidence that removal to the hospital does prevent the spread of disease in the family In Providence it appears that removal to the hospital cuts down secondary cases one third

Active Immunization

Smith (1910) summarized the reports, mainly in Russian describing active immunization with Gabritschewsky's (1906, 1907) vaccine a mixture of toxin and streptococci About 50,000 inoculations were done from 1907 to 1909, largely in villages in the presence of epidemics The reactions were severe, but the results seemed promising unfortunately Gabritschewsky died in 1907 (His obituary appeared in the same issue of the Berliner klinische Wochenschrift, XLIV, 586, May 6 1907 as his discussion of the streptococcal scarlatinal vaccine) Without him the complexity of the problem was too great and the methods too crude to permit these small successes to overcome the general disbelief in the streptococcal etiology of scarlet fever

Conditions are quite different now The ground has been prepared by Park s great work in the prophylaxis of diphtheria Scarlet fever and diphtheria both are known as bacterial toxemias There is a general acceptance of the etiological role of *Streptococcus hemolyticus* Dick and Dick (1924 a, b 1925 c 1938) have developed a test to measure susceptibility or immunity methods of standardizing toxin and have succeeded in corroborating Gabritschewsky and his school as to the possibility of active immunization against scarlet fever All that remains is to determine the practical value of active immunization

This active immunization is proving to be a more difficult problem than was the case for diphtheria First, the current scarlatinal toxemia is mild, secondly, more injections and more reactions accompany scarlatinal toxin, and no satisfactory toxoid is available, thirdly, hemolytic streptococci have pyogenic and sequelogenic properties, which at best are merely indirectly opposed by antitoxic immunity

It is impossible to foretell what effect active immunization may have on the carrier state in a community Among nurses who had been actively immunized, Kinloch Smith and Taylor (1927) reported an increase in the incidence of "scarlet fever without rash" and Benson (1928) on the other hand found a decrease in streptococcal tonsillitis in a similar population of immunized nurses

Indications for Active Immunization — It is logical to believe that a given scarlatinal infection would be milder in the presence of antitoxic immunity Hence when anyone wants active immunization, it is reasonable to employ the procedure of Dick and Dick since it has inconveniences but no real contraindications

The more severe the current type of scarlet fever is and the greater the risk of contracting it the stronger the indications They are greatest among the personnel of hospitals for infectious disease The method is not ready for general advocacy and widespread publicity

Procedure in Active Immunization — When active immunization is considered,

the susceptibles are detected by the Dick test and then are given a series of subcutaneous injections of scarlatinal toxin The toxin is much less destructive to tissues than diphtheria toxin hence sufficient dosage of the unneutralized toxin may be injected without causing harm Dick and Dick (1938) advocate beginning with 650 skin test doses followed at weekly intervals by a second dose of 2 500 skin test doses a third dose of 10 000 skin test doses a fourth dose of 50 000 skin test doses and a fifth dose of 100 000 to 1 0 000 skin test doses A toxin suitable for immunization purposes should contain at least 50 000 to 100 000 skin test doses per c c before dilution

The larger immunizing doses of toxin give a higher degree of immunity in a *higher percentage of susceptible persons In much of the work reported smaller* doses have been used We have not been able to verify the results of those who claimed negative skin tests in 85 per cent after a maximum dose of 3 000 skin test doses of toxin Nor have reports as to the protective value of ricinoleated toxin described by Larson and his co-workers of formalized preparations of scarlet fever toxin or of scarlet fever toxin in ointment for inunctions been verified All the evidence available indicates that scarlet fever toxin does not form an antigenic toxoid on treatment with formaldehyde by the method used in preparing diphtheria toxoid. Formaldehyde partially detoxifies the scarlet fever toxin but the detoxified portion is not antigenic Such immunizing value as formalized preparations of scarlet fever toxin retained is dependent on the unmodified toxin remaining in them and not due to a toxoid

Reactions — In the routine use of toxin for active immunization there may be general symptoms with fever and a scarlatinal eruption in those highly susceptible These reactions are not dangerous but they are obviously objectionable and confusing in the matter of diagnosis

In part such reactions may be avoided according to Dick and Dick (1938) by modifying the dosage of toxin in persons who give large bright reactions to the original Dick test If the skin reaction is 30 mm in any diameter it is best to begin with one half of the first dose and follow this a week later with a full dose proceeding from this point with the regular dosage If the skin reaction is 40 mm or more in any diameter and bright in color one fourth of the first dose may be given and a week later a full first dose injected continuing from this point with the regular dosage

Severe general reactions may cause one or more of the following symptoms repeated vomiting marked diarrhea and fever up to 101 F for 48 hours Severe reactions are due to too rapid absorption of th toxin and indicate that epinephrine should be injected with the subsequent doses The epinephrine 0 2 to 0 3 c c of a 1 1000 solution is taken up in the same syringe with the toxin and injected with it As a rule reactions after the last and largest dose are fewer and milder than after the smaller doses

Dick and Dick continue their discussion of reactions "There are two other types of reactions infrequently encountered in children and not common in adults These are urticaria and joint pains

Urticaria is caused by previous sensitization to protein contained in broth Urticaria may occur in 6 per cent of the young adults immunized against either scarlet fever or diphtheria in training schools for nurses and medical schools owing to the fact that most of them have had one or more courses of immunization with diphtheria toxoid and other vaccines before entering With the use of scarlet fever toxin prepared in the preferred medium the incidence of urticaria in this group is reduced to 1 per cent , in those, who develop urticaria with this product, the immunization may be continued with the purified toxin without the development of urticaria There is no anaphylactic shock associated with the urticaria

'The other type of reaction which is not controlled by proper methods of injection consists of joint pains Healey (1937) reported a well controlled series of experiments which established the fact that joint pains may occur in persons who have had previous rheumatic infection or traumatic joint injury, and that they are due to the toxin itself, not to a protein reaction The joint pains are transient They never initiate an attack of rheumatism but the patient is inconvenienced by them the temperature may go above 101° F but returns to normal within 48 hours

Retest — Two weeks after the last immunizing dose another skin test is made, using 0 1 c c of the skin test solution, or one skin test dose, on the right arm and 0 2 c c or two skin test doses on the left arm If the reaction on either arm is positive, the fifth dose is repeated

In this way sufficient immunity is established so that there can be some falling off from the highest titer of antitoxin in the blood and enough immunity still retained to protect against an attack of scarlet fever

Duration of active immunity as well as the degree of immunity, depends upon the amount of toxin injected Retests made at intervals up to 12 years indicate that more than 90 per cent of those immunized to the point of an entirely negative skin reaction with the dosage previously described retain their immunity Between 5 and 10 per cent may require a second immunization Loss of immunity when it occurs usually happens by the end of one year after immunization If the skin test is slightly positive or moderately positive at this time, reimmunization may be accomplished by injection of the first third and fifth immunizing doses of toxin But if the skin reaction has become strongly positive, it is best to administer the five doses of toxin'

Zinsser, Enders and Fothergill (1939) concluded that, as yet there is no adequate proof of a satisfactory scarlatinal toxoid for the active immunization of patients having scarlet fever

Management of Outbreaks of Scarlet Fever

Outbreaks of scarlet fever are of different types In most very little can be *accomplished but in some there is much to be gained by appropriate methods* No specific rules can be laid down but crowding favors contagion Milk or food borne epidemics may be recognized by their explosiveness their increased age incidence their relation to one milk supply They can be checked by excluding the offending source or by pasteurization of the milk

Chapin (1913) observed that when the first child with scarlet fever in a family was hospitalized there was a one third decrease of secondary cases Kinloch *Smith and Taylor (1927) stated that the occurrence of return cases might be* rendered less likely by the active immunization of susceptible members of the family immediately after the first case was admitted to the hospital

In English public schools a School Epidemics Committee (1938) has analyzed data collected during the first five years of inquiry covering 22 166 boys and 7 600 girls in 31 schools In respect to scarlet fever it was noted that Although only 5 to 10 per cent of our population were protected by previous attack scarlet *fever showed less inclination to spread than any other infectious disease except* diphtheria Of 49 outbreaks among boys only 11 or 22 4 per cent gave an attack rate of 1 0 per cent or over and only 2 out of 12 or 16 7 per cent among girls The highest attack rate in any epidemic among the boys was 3 5 per cent in 1930 while among the girls school H/E experienced a ratio of 4 0 per cent in 1932 Six small outbreaks are illustrated and all show a tendency to be drawn out until the end of the term the *disease being apparently unable to spread widely or to die out*

There was a tendency for the disease to appear in the same school in successive terms In school R/B scarlet fever was reported in seven successive terms *for 1931 to 1933*

There was a striking difference The boys reported a total of 271 cases and the girls only 27 allowing for the fact that the boys outnumbered the girls by nearly 3 times we might expect 81 cases among the girls had the two populations been equal Hence it appears that the boys reported more than three times as many cases as the girls

We can offer no explanation of this sex difference nor for the apparent in *ability of the disease to attain epidemic proportions From the knowledge gained* by other workers by means of the Dick test we may presume that a certain number of our population although not protected by previous attack had become immune with advancing age but except for one school we do not know what proportion was constituted by immunes

Active immunization against scarlet fever was done in only one school Various factors including the comparative inability of the disease to spread widely

when left to its own devices, are sufficient to strengthen our opinion that the advantages of artificial immunization as practiced at present are not sufficient to compensate for the labor and disability incurred during the process It should be remembered that these remarks apply exclusively to the public schools in which conditions do not apparently favor the development of widespread epidemics of scarlet fever but in certain environmental conditions, such as a fever hospital in which the risk of infection is very high, the immunization of susceptible nurses has been performed with brilliantly successful results"

Passive Immunization

Except in unusual circumstances prophylactic passive immunization with antitoxin is an undesirable procedure The probability of infection is not very high and if one is on the lookout, the chances for cure are excellent If, on the other hand, it should develop three or four weeks after the passive immunization, the individual may be sensitive to horse serum and difficult to treat If passive immunization must be used, theoretically at least, it would be best to use human serum from a donor negative to the Dick test The human antitoxin should produce an immunity of longer duration and should not lead to serum sickness or sensitivity to horse serum No rules are available for dosage but it would be reasonable to expect good results from the intramuscular injection of 50 to 100 c c of serum from a Dick negative individual In some large cities convalescent human serum is available (Thalhimer, 1938)

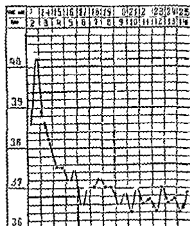
As a prophylactic in scarlet fever sulfanilamide was mentioned favorably by Sako Dwan and Platou (1938) and sulfonamides since then have been used extensively in the control of streptococcal infections among military personnel The results appear favorable except for evidence of possible development of sulfonamide resistant hemolytic streptococci (Rantz, Randall, Spink and Boisvert 1946) The use of sulfonamides in rheumatic subjects as a prophylactic against streptococcal infections has been described as successful by Thomas and France (1939) and Coburn and Moore (1939) Their results have been substantiated by a number of investigators

TREATMENT

Specific Therapy

Moser (1902) and Savchenko (1905), respectively had scarlatinal antistreptococcal sera and scarlet fever antitoxin which were effective in scarlet fever, Fig 31, Menshikov (1905) Moser s horses were immunized with strains recovered from the heart's blood of fatal human cases Control serum from normal horses

as well as Marmorek s and Aronson s streptococcal antisera showed no thera peutic power Both Moser s and Savchenko s antisera effected a critical cure with rapid disappearance of the rash in severe acute scarlet fever and had little or no effect in late septic complications Table XI shows the results of Moser s (1902) first 84 cases 81 were chosen as severe among 699 admitted to the Chil dren s Hospital in years In view of this large experience his success was worthy of note and Escherich and Schick (1912) stated that the serum should be used in severe cases before the 4th day


Fig 31 Satisfactory treatment of severe scarlet fever with Savchenko s scarlet fever antitoxin (from Men shikov 1905)

These early successes died out To-day after having been unearthed by Park (1925 b) *it seems peculiar that Savchenko s work was* not followed up It is true that he stated in his premise that the primary cause was un known but he believed that a streptococcal toxemia was an important element of scarlet fever He had a method of demonstrating the toxin in filtrates of broth cultures namely by subcutaneous injection in horses Also he developed a method of comparing anti toxins This was by their protective action in rabbits against live cultures of scarlat inal streptococci a method which Parrish and Okell (1927) used successfully Perhaps these methods appeared impractical in 1905 when so few authorities held that scarlet fever might be a streptococcal disease and most were thinking of an unknown virus as the essential cau e perhaps the therapeutic dose of 100 and 200 c c was too cumbersome perhaps severe scarlet fever became uncommon enough to prevent the standardization of the antitoxin perhaps knowledge of the results was not sufficiently diffused out side of Russia At any rate the specific antistreptococcal therapy of scarlet fever was gradually abandoned until Dochez saw the possibility of detecting scar latinal antitoxin by means of the Schultz Charlton rash extinction phenomenon Dochez s antitoxin was made by the time that Mair (1923) had explained the Schultz Charlton reaction and had predicted that the experimental production of the blanching would reveal the true nature of scarlet fever Dochez (1924 a b) developed an ingenious method of inoculating scarlatinal streptococci into horses This consisted in preparing in the horse a subcutaneous nodule of agar and inject ing living scarlatinal streptococci into it The horses did not kill the streptococci and the streptococci did not kill the horses but produced local abscesses and the outcome was a highly potent scarlatinal antitoxin In the fall of 1923 Dochez

TABLE XI

RESULTS OF TREATMENT WITH MOSER'S (1902) ANTISCARLATINAL SERUM IN HIS FIRST 84 CASES WHICH WERE ARRANGED ACCORDING TO THE PROGNOSTIC CLASSIFICATION OF ESCHERICH'S CLINIC

Day of Treatment	Total Cases Treated	Group I			Group II			Group III			Group IV		
		Cases	Deaths	% Mort	Cases	Deaths	% Mort	Cases	Deaths	% Mort	Cases	Deaths	% Mort
1	2	1						1					
2	15	1			6			3			5		
3	17	2			1			8	1	13	6	1	16
4	18				5			7			6	3	50
5	19	1			3			6			9	6	67
6													
7	3							1			2	1	50
8	5				1			2			2	2	100
9	4										4	2	50
10	1				1								
Totals	84	5			17			28	1	4	34	15	44

* Groups I and II were mild and moderate Groups III and IV were severe and very severe the last with a fatal outcome expected

sent his antitoxin to various clinics and soon the presence of scarlatinal antitoxin in it was demonstrated by Blake Trask and Lynch (19 4) Birkhaug (1925 a) and others Shortly Blake (1924) showed that the antitoxin would cure scarlet fever Cure was accomplished by the neutralization of the toxin in the blood and by the prompt establishment of an excess of circulating antitoxin This led to the following (a) a prompt cure of uncomplicated scarlet fever (b) a prompt cure of the specific toxic phase of the disease in septic cases (c) no result in post scarlatinal sepsis

Evidently the mechanism of the curative action of the serum resides in the neutralization of the specific toxemia present during the exanthematous stage of scarlet fever These conclusions as they relate to the therapy of scarlet fever have been amply supported by Birkhaug (1925 b) Park (1925) Dick and Dick (1925 b) Thenebe (1926) and others

Results of Treatment with Antitoxin — In certain epidemics it has been possible to show the life saving effects of the antitoxin (Toyoda and associates 1929 Mersol 1929 and others) However in the usual mild scarlet fever of to-day the most that can be demonstrated statistically is a diminution of complications and sequelae This has been done by giving and withholding antitoxin in alternate cases (Harries 1927 Veldee and associates 1931)

Topley and Wilson (1936) stated that there is clear evidence that antitoxic serum has a significant therapeutic effect on the toxic manifestations of scarlet fever and suggestive evidence that it may contrary to our prior expectations lessen the frequency of those complications that are due to the invasive action of the streptococci

Methods of Producing Antitoxin — Following the production of a potent antitoxin by Dochez other methods of preparation were shown again to be available The original method of Savchenko (1905) the subcutaneous injection of toxin was adapted by Dick and Dick (1924 d) and they (1925 b) developed a method of measuring antitoxin which was more convenient than the rash extinction test Other individuals used the combined injection of broth culture (toxin) and streptococci as Moser had done Most manufacturers using toxin for immunization do not use a filtrate but the supernatant fluid after centrifuging the broth cultures Some who use Dochez s method of the agar nodule also inoculate their horses with toxic filtrate or centrifugate When bacteria are included in the immunizing processes antibacterial bodies appear These might be of therapeutic value but there is no evidence that they are All the methods produce scarlatinal antitoxin As yet the best method has not been determined but whatever the method of manufacture the virtue of antiscarlatinal serum is standardized by its content of scarlatinal antitoxin

Accordingly it is important that Wadsworth and Coffey (1935) found that some scarlatinal streptococci call forth antitoxins which neutralize toxins from

many scarlatinal strains, while others produce antitoxins, which neutralize toxins from but few strains Thus, Wadsworth (1929) described strains of wide and of narrow antigenic valency Dochez's N Y 5 is a strain of wide valency and is much used here and abroad Coffey (1938) found that antitoxin made by N Y 5 called 165 by her, neutralized the toxins of 85 per cent of 450 human pathogenic hemolytic streptococci A pool of two scarlatinal antitoxins from N Y 5 and either 1 of 2 other choice strains neutralized 98 per cent of toxins from 217 strains

Standardization of Scarlatinal Antitoxin — The standardization of scarlatinal products has been difficult and inaccurate because there is more than one scarlatinal toxin and no highly satisfactory test animal A practical method of comparing antitoxins has developed from the neutralization of skin tests in rabbits by Frazer and Plummer (1930) and Veldee (193), and it should be possible to have a good antitoxin available to all

Blake and Trask (1925 a b c) standardized antitoxins by finding the smallest dose which would produce the Schultz Charlton blanching test This was called the minimal blanching dose The method requires a supply of patients with a good rash but not sick enough to require a therapeutic dose of antitoxin and, therefore is too cumbersome and is impractical for general use Nevertheless the method is of value in the clinic (Friedemann and Diecher, 1928) because it shows whether or not small doses of the antitoxin being used are, in fact, neutralizing the prevailing toxin

Moreover, the method has been subjected to the following critical trial (Blake and Trask 1925 a b c) The minimal blanching dose was determined for ten lots of antitoxin, which were used for the intramuscular treatment of a series of 43 children and adults with scarlet fever of varying severity The presence of toxin and antitoxin in the blood before and at intervals after treatment was determined, and the results were correlated with the therapeutic effect The data appear in Table XII and may be summarized as follows 1 The therapeutic efficacy of a serum is proportional to the antitoxin content of the serum 2 An antitoxin to be of value in dosage of reasonable volume should contain more than 12,500 minimal blanching doses per c c

Dosage — From table XII it may be seen that an adequate intramuscular dose for moderate and severe cases was from 30 to 95 c c of an antitoxin which contained at least 1 500 minimal blanching doses per c c As indicated in the table, this was estimated to be equivalent to enough antitoxin to neutralize 300,000 to 950 000 skin test doses of toxin or to 3 000 to 9 500 units in the terms of 1925 Since then the amount of toxin in a unit has been halved Dyer (1928), and the proper doses are respectively 6 000 to 19 000 units according to the current standards of the National Institute of Health, Washington, D C and of the Health Organization of the League of Nations

This dosage is in conformity with the experience of Park (1925 a, b) at the

TABLE XII

St dies on Do a e t i Ten Diffe ent Lots of Sca lat nal Antitoxin of Varying Content p r Cub c Centimeter of Serum
(From Blake and Tra k 1925 a b c)

Antitoxin lot	M B D per c c	Case	Age	Clinical severity	Amount of serum c c	Total** units antitoxin injected	Type of rash serum before treatment	Antitoxin in patient's serum before and after treatment — Day of disease					Summary	Therapeutic effect
										4	5	6		
D h z (ra)	62 500+	E H		M l sev	5	500+								C l
Dxch z ( )	(00+	S L	9	S t septic		500+	++							C red
D h z (c nc)	6 500+	M T	2	M d se	5	2 500+	–	–	+++				++	Cured
Dxch z (conc)	500+	K A	20	M 1 se	5	500+	+							C ed
D chez (conc)	500+	O S	3	Ext sev to septic	5–5	5 000+	+++				+++	++	++	Cur d
D h z (uncon)	500+	9	½ o	M ll 5 mod	o to 50	000 t 5000+	– t +++						++	C re l
(S mma y)		9	6–33	M ll 1 mod	5 t 4	500 to 4000+	– t ++						t ++	Cur l
Doch (u con)	500+	6	½–50	S 5 se r	15 to 9	1100 t 9500+	+ t ±+						++	Cu d
(Summary)		6	3 5	S 13 se e	o t 135	1000 to 13300+	– ++						t ++	Cu l
A 77 u conc)	2 500	R B	6	M ll	35	3 400	+						+	Cure l
A 7 (u o c)	2 500	J K	5	M l sev	40	4000	++			–	+		+	Cur l
A 77 (u n)	500	M K	5	S s	4	2000	+		+				+	Cur d
A 5 5 (un conc)	500	S J	2	Mod se	40	4 000	+		+				+	Cur l
357–9 (u conc)	500+	F J	8	Mod se	3	00+	++		–	+			+	Cu l
A 5 (nc)	500+	J K	9	M 1 se	4	500+								Cu l
A 5 (con)	500+	H 3	5	M ll	35	00+	+++				–	±	±	?
A 5 (conc)	2 500+	C M		S r	3	300+	+				–		–	N e
36 –9 (uncone)	2 500	F B	0	M ll	5	00	–		–	–			–	N ne
U S (c)	2 500	E W	7	M ll	40	400			–	–			–	N n
U S (conc)	2 500	W S	9	M ll	49	500	–							None
U S (conc)	500	K S	23	M ll	4	800	+		–	–	–		–	None
35 –9 (nc nc)	500+	3	4 9	M ll	40	0+			t*		t			None
375 9 (unconc)	500+	B B	6	Mo l seve	4	0+								None

* In l tes t eatm nt w th antit x n

M B D = M n m l blan h ng dose

O nt of ant t x n uff c nt to n utr lize too k n te t doses f t x n Th val g e n t th column ar an p x m at on For p ese t usag th figur n th lum h ul l e d ubled

many scarlatinal strains while others produce antitoxins, which neutralize toxins from but few strains Thus, Wadsworth (1929) described strains of wide and of narrow antigenic valency Dochez s N Y 5 is a strain of wide valency and is much used here and abroad Coffey (1938) found that antitoxin made by N Y 5 called 165 by her neutralized the toxins of 85 per cent of 450 human pathogenic hemolytic streptococci A pool of two scarlatinal antitoxins from N Y 5 and either 1 of 2 other choice strains neutralized 98 per cent of toxins from 217 strains

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Moreover, the method has been subjected to the following critical trial (Blake and Trask, 1925 a b, c) The minimal blanching dose was determined for ten lots of antitoxin which were used for the intramuscular treatment of a series of 43 children and adults with scarlet fever of varying severity The presence of toxin and antitoxin in the blood before and at intervals after treatment was determined, and the results were correlated with the therapeutic effect The data appear in Table XII and may be summarized as follows 1 The therapeutic efficacy of a serum is proportional to the antitoxin content of the serum 2 An antitoxin to be of value in dosage of reasonable volume should contain more than 12,500 minimal blanching doses per c c

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inadequate antitoxin The evidence for this consists in statements in the reports of unsatisfactory fading of the rash If the treatment had been adequate the rash would have faded promptly In other instances the scarlet fever has been mild and the serum sickness has been too severe to justify the antitoxin (Toomey and Dolch 1928)

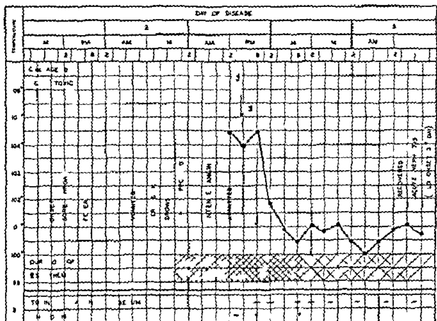


FIG 32 C M Severe scarlet fever toxic severe angina and ulcerative tonsillitis Critical cure with Dochez s antitoxin Neutralization of specific toxemia and establishment of excess of antitoxin in blood four hours after intramuscular treatment Mild acute nephritis on 31st day

Immunity after Therapy with Antitoxin — Five to 18 months after scarlet fever Davies (1926) found an unduly high incidence of positive Dick tests in cases which had been treated with antitoxin However some of the positives represented pseudo-reactions and there is further evidence that this is not a contra indication to serotherapy because after a wide experience Lichtenstein (1931) observed fewer relapses in cases treated with convalescent serum or with scarlatinal antitoxin than in cases treated without serum

Current Position of Antitoxin in Therapy — General reviewers such as Topley and Wilson (1936) and Zinsser Enders and Fothergill (1939) make it clear that the beneficial results with antitoxin in scarlet fever are reproducible and have been obtained by many workers The favorable reports are consistent they describe the critical cure of the specific erythrogenic toxemia and subsequent

Willard Parker Hospital He felt that sufficient antitoxin to neutralize 200 000 to 1 000 000 skin test doses of toxin, 4,000 to 20,000 units, would cover the range of dosage for all cases However, Park advised the highly efficient intravenous route of administration This route is to be recommended from Bank ' (1933) experience in treating 1,204 cases in which usually there was a critical recovery in 6 to 24 hours The edema disappeared from the primary pharyngeal lesion in 12 hours and the rash faded in 12 to 24 hours The incidence of later scarlatinal complications was about 4 per cent, and there was one death It was not attributed to the serum

Commercial interests are apt to use the conveniences of concentration as selling points Obviously, concentration is possible and desirable, small volumes and decreased serum sickness are good features On the other hand, concentration magnifies the difficulties of standardization, which are hard enough because of immunological variability among toxins and other technical reasons These things emphasize the fact that the essential requirement of good antitoxin is high potency and wide valency before concentration is attempted After the best possible serum has been attained, concentration may be used to make its good qualities more convenient

Clinical Results with Antitoxin — Adequate dosage will cause a prompt cure in uncomplicated scarlet fever (Fig 31) In cases with marked toxic and septic features treated early, the specific toxemia is cured promptly (Figs 32 33 and 34), and the septic processes may recede quite rapidly (Fig 33) Cure of the specific toxemia consists in subjective and objective improvement, critical fall of the vital signs and rapid fading of the rash A sharp drop to normal in the leucocyte count, following critical cure with antitoxin, was noted by Birkhaug (1925 b) *Streptococcus scarlatinae* persisted at least three weeks in throat cultures from scarlet fever patients whether they were treated or not (Nicholls 1926)

Adequate treatment decreases the incidence of subsequent complications The mechanism of this is not clear presumably it depends on the beneficial effect of the antitoxin on the primary lesion in the throat, which ordinarily with edema, erythema and sometimes necrosis shows well marked evidence of the local action of the toxin In some septic cases neutralization of the toxin is not enough, and they may have a prolonged febrile course after treatment (Fig 34), or they may become progressively sicker and die with spreading sepsis (Figs 16, 17 and 35) With treatment in the second week of the disease after the rash has faded, no beneficial effect from the antitoxin has been observed (Figs 10, 15)

Failures with Antitoxin — Disappointing results with antitoxin have been reported Trask and Blake (1932) had failures in a series of 3 cases and this led to the incrimination of a new type of scarlet fever toxin Some other workers have had disappointing results (Weech 1931, and others) Few of these failures have been explained adequately, some without doubt may have been due to an

inadequate antitoxin The evidence for this consists in statements in the reports of unsatisfactory fading of the rash If the treatment had been adequate the rash would have faded promptly In other instances the scarlet fever has been mild and the serum sickness has been too severe to justify the antitoxin (Toomey and Dolch, 1928)

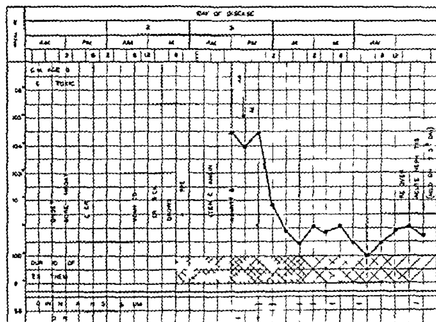


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decreased incidence of septic complications such as purulent otitis media and sinusitis A decrease in sequelae probably occurs, but this is less certain, first, because there is much epidemic variation among sequelae, and secondly, some authors do not differentiate between complications and sequelae The antitoxin is used in large municipal hospitals here (Lucchesi and Bowman, 1934, Toomey

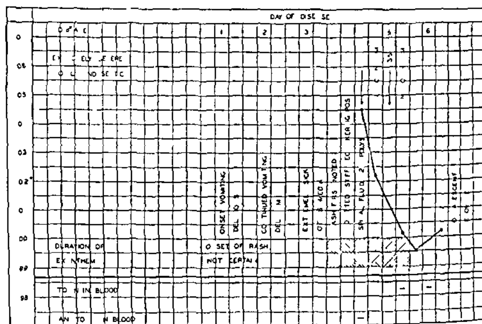


FIG 33 J D Severe scarlet fever toxic and septic with sympathetic meningitis. Critical cure Antitoxin was given intramuscularly Prompt subsidence of septic processes Scarlet fever toxin in blood before treatment therapeutic neutralization of toxin and establishment of excess antitoxin in blood by time of second treatment which thus proved to be unnecessary

and Baker, 1938) and in large hospitals abroad (Harries 1939 and Rolleston 1939) Antitoxin is not used widely in private practice in large cities in the north eastern section of the United States

Indications for Treatment —The indications for antitoxin depend on the severity of the case and nature of the epidemic In mild cases and in mild epidemics it is impossible to decide what total benefit may be expected from antitoxin because the serum sickness may be especially disturbing It seems best not to use serum in mild cases (Toomey and Dolch 1928) A reasonable plan is to use antitoxin in all cases more than mildly sick in the first three days and to use it in all severe cases while the rash still is well marked

The rash is the index of the presence of the specific toxemia and consequently forms one indication for treatment after the rash has faded, antitoxin no longer need be administered for the patient then has made his own excess of antitoxin

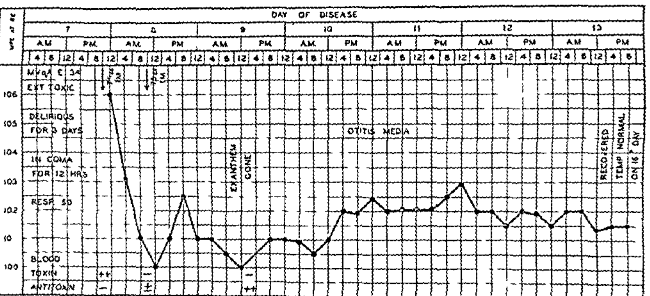


Fig 34 M S Severe scarlet fever toxic and septic scarlet fever toxin in blood before treatment Critical cure of specific toxemia with establishment of excess antitoxin in blood after intramuscular injection of antitoxin Second dose of antitoxin proved to be unnecessary Recurrence of old otitis media which subsided gradually

While the rash is present, the extent of the septic processes measures the amount of free toxin in the patient and hence indicates the dosage required The extent of the septic involvement present often is underestimated in cases with infection of nasal and paranasal sinuses Hence, with any noteworthy nasal or post nasal mucopurulent discharge patients should be considered much sicker than they appear to be and should receive large doses of antitoxin

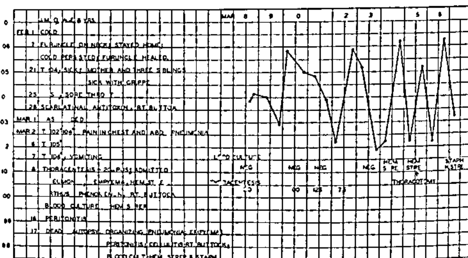


FIG 35 J M Fatal post scarlatinal pneumonia arthus phenomenon at site of intra muscular injection of antitoxin No growth in first four blood cultures 5th and 6th positive for hemolytic streptococci and 7th positive for hemolytic streptococci and staphylococcus Patient treated before days of sulfanilamide

The full therapeutic dose should be estimated and given at once in a single dose Intramuscular injection is satisfactory in most cases, and the site of choice is into the anterior or lateral aspect of the mid thigh In serious, and perhaps in moderate cases the intravenous route is best (Banks 1933) This is a method for use in hospitals

Indications for a second dose of antitoxin consist in the failure of the tempera ture and pulse to fall, lack of subjective improvement and the absence of beginning fading of the rash 12 to 18 hours after the first treatment In later toxic and septic cases failure of the rash to fade is the most satisfactory indication for re peated treatment Although the fever usually shows a distinct drop after treat ment in these cases it may persist usually at lower levels, because of the septic processes for some time, even though there is an excess of antitoxin in the blood of the patient Failures should not happen, and they suggest immediately that the antitoxin may be of inferior strength or valency

Serum Reactions — Serum sickness is particularly undesirable because of the septic complications and sequelae of scarlet fever There is some reason to believe

that serum sickness may aggravate septic processes (Fig 31 and Chandler and Hartshorn 1933) Experimentally anaphylactic shock in rabbits has been found to augment a hemolytic streptococcemia (Burn Chandler and Hartshorn 1934) However relapses and recurrences were features of scarlet fever before the use of serum in its treatment

Precautionary Measures in Serotherapy — The usual care should be taken before the injection of antitoxin An authoritative description of the precautions is taken from Zinsser Enders and Fothergill (1939)

Reactions may occur in spite of every precaution but their frequency may be diminished by the observance of certain measures

History — Before the injection of serum all patients should be questioned about their having had asthma hay fever eczema urticaria angioneurotic edema or hypersensitiveness to horse dander or horse serum Serum should not be given *intravenously* to those with such a history

They should also be questioned as to whether they have previously had horse serum (diphtheria tetanus or other antitoxin antimeningococcic or antipneumococcic serum diphtheria toxin antitoxin mixture etc) If the history is positive the administration of serum should depend upon the outcome of the tests described below

A reliable history is essential Young patients or those who are very ill may be unable to give a proper history in which case it must be obtained from *other members of the family*

It is always important to impress upon the patient or those responsible for him that they must remember the fact that serum has been given and the time at which it is administered for report to the physician should another serum injection ever be called for in the future At the same time the difference between *vaccine and serum must always be made thoroughly clear since even physicians* not infrequently confuse these terms

Tests for Hypersensitivity — At least one of the following tests should be used in all cases where serum is to be administered intravenously A test is also desirable when serum is to be given by any other route

1 *Ophthalmic Test* This is done by putting one drop of serum (undiluted or diluted 1–10) into the conjunctival sac of one eye A positive reaction is indicated by itching water and a diffuse reddening of the eye within 30 minutes An extreme reaction may be controlled by the instillation of a few drops of epinephrine (adrenalin) 1–1 000 dilution

This test is of no value in young children for they may wash out the serum by crying

2 *Skin Test* — Have at hand ready for use a syringe containing 1 c c epinephrine (adrenalin) 1–1 000 dilution A further supply of epinephrine should be within reach

While the rash is present, the extent of the septic processes measures the amount of free toxin in the patient and hence indicates the dosage required The extent of the septic involvement present often is underestimated in cases with infection of nasal and paranasal sinuses Hence, with any noteworthy nasal or post nasal mucopurulent discharge patients should be considered much sicker than they appear to be and should receive large doses of antitoxin

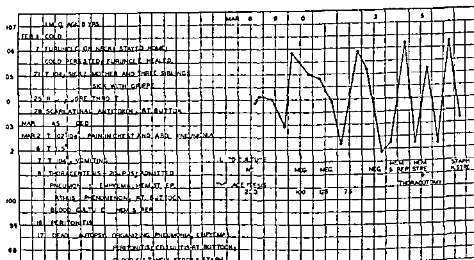


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the dose may be doubled and so long as no reaction intervenes further doses are given at 15-30 minute intervals using twice the amount given at the preceding dose until a dose of not less than 1 c c of *undiluted* serum has been given subcutaneously without reaction

These directions should be taken to represent only an example of average procedure No precise rules can be laid down for all cases The responsible physician should be familiar with the possible reactions that may occur and should adjust quantities and time intervals according to judgment in the individual case

Further treatment depends upon the kind of serum to be given and the route of administration For subcutaneous intramuscular or intraspinal administration the full dose may be given 30 minutes after the last subcutaneous dose

For intravenous treatment more caution is required The first intravenous dose following the last subcutaneous one of at least 1 c c of undiluted serum should not exceed 1 c c of serum diluted 1-10 This may be followed 20 to 30 minutes later by twice as much serum and further doses doubling in amount each time may be given at similar intervals *Inject the serum slowly not faster than 1 c c per minute*

If any injection is followed by edema urticaria or respiratory distress the symptoms may be relieved by epinephrine If more serum is given the next dose of serum should not be larger than the previous dose (the one causing the reaction) and should not be given until at least 30 minutes later If this also causes reaction no further serum should be given intravenously

Convalescent Serum

Reiss and Jungman (1912) had good therapeutic results with convalescent human serum and this has been confirmed by Moog (1921) Gordon (1933) Hoyne and associates (1935) and others The essence of the method consists in an adequate intravenous dose Normal human serum is effective if taken from Dick negative donors and if used in doses of 100 to 200 c c The beneficial results are attributable to the scarlatinal antitoxin According to Davies (1926) there may be about 20 units of antitoxin per c c of serum in those whose skin reacts negatively to four skin test doses of toxin Consequently the intravenous injection of 100 to 200 c c of this serum would be a therapeutic dose At this time use of the gamma globulin fraction of pooled adult serum has not been shown to materially alter the course of scarlet fever

Special Measures

Loss of fluid and electrolytes by vomiting or diarrhea may become a vital matter quickly and require repeated parenteral administration of water glucose

'0 1 c c of physiological salt solution is injected as a control *into*, not under, the skin of the anterior surface of one forearm and 0 1 c c of a 1-100 dilution of normal horse serum is similarly injected in the other forearm The dose used for an intracutaneous test is often even larger than the one just mentioned, some observers using as much as 0 1 c c of a 1-10 dilution In cases in which the history is one which indicates probable hypersensitiveness, it is best to begin with smaller doses The injected fluids each produce a small white wheal at the site of injection both of which disappear within a few minutes if the test is negative (The wheal produced by the serum may not disappear quite so quickly as that due to the saline)

In sensitive patients the skin elevation at the site of the serum injection rapidly enlarges within 5 to 20 minutes and becomes urticarial in appearance with a surrounding zone of erythema The size of the wheal is perhaps a rough indication of the degree of sensitivity In strongly positive tests pseudopodial extensions of the central wheal are noted Positive skin tests ordinarily subside within an hour or two

Interpretation of Tests —Although the tests described do not always give an accurate indication of hypersensitivity these tests, together with the following rules are suggested as a guide to treatment

1 Do not give serum *intravenously* to patients with (1) a positive history of asthma hay fever, etc or (2) a positive or questionably positive ophthalmic test, unless the therapeutic indications for serum are urgent as in malignant diphtheria, meningitis, etc

2 Do not give serum *intravenously* to patients with positive skin tests, unless they are first desensitized' by the method outlined below or a similar one

"3 Serum may be given by any route in patients with negative histories and tests If given intravenously the serum should be warmed to body temperature and given slowly (1 c c per minute) In giving the first intravenous dose it is desirable to wait 15 to 30 minutes after 1 c c has been given before further amounts are injected

"4 Patients should be kept under observation for three quarters of an hour after any administration of serum

Desensitization —Hypersensitive persons may be partially desensitized by the repeated administration of very small doses of serum The method is not uniformly successful but should not be omitted when history or tests indicate sensitiveness

'Epinephrine (adrenalin) 1-1 000 dilution, must be at hand in a syringe and ready for use should a reaction occur

'Administration of serum is begun with subcutaneous injections of dilutions of normal horse serum or of the serum to be used for treatment The initial dose is 0 005 c c (0 5 c c of a 1-100 dilution) If no reaction occurs within 15 minutes,

severe It is effective in puerperal sepsis meningitis erysipelas streptococcal pneumonia and empyema and streptococcal bacteremia However therapeutic doses are not effective in streptococcal tonsillitis or pharyngitis and do not lead to the rapid cure of the scarlatinal toxemia or cause an accelerated fading of the rash Also the drug is ineffective in scarlatinal sequelae Thus good results are obtainable when streptococci are active in a lesion within the body where they can be bathed in an effective concentration of the drug When the streptococci are on surfaces, as on the pharyngeal mucus membrane or when the lesion is the late response to departed streptococci, then sulfadiazine has not appeared effective Further experience may lead to the routine early use of the drug because it may prevent the spread of the primary lesion and thereby reduce the incidence of complications and sequelae (Peters and Havard, 1937) In early severe cases the combined use of antitoxin and sulfadiazine is logical and in a severe epidemic this procedure most likely will receive an adequate trial At the moment indications for the drug in scarlet fever are given below and some illustrations of the effect of sulfanilamide are shown in Fig 36 Leading indications for the use of a sulfona

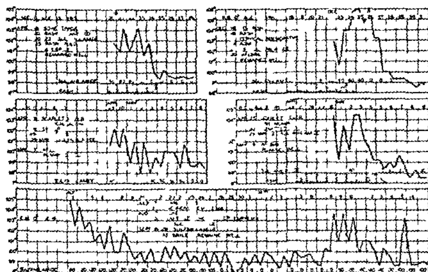


Fig 36 Sulfanilamide therapy and some aspects of scarlet fever Case M F Uncomplicated scarlet fever treated on 2nd day without obvious effect Case R B Moderate scarlatinal cervical adenitis treated on 6th day with toxic reaction recovery was rapid on stopping the drug Case L H. Post scarlatinal cervical adenitis, treatment in 4th week Result was satisfactory but not dramatic Case B C Scarlet fever and pneumonia treated on th day response satisfactory but not dramatic Case E M Post-scarlatinal empyema Recovery without thoracotomy highly satisfactory response to sulfanilamide Sulfanilamide by mouth, daily dosage shown in grams. Blood levels ranged between 5 and 11 mgm. per 100 c c. Lower value is much less than considered optimal.

and salts In patients with severe angina or with cerebral symptoms special attention must be given to maintaining a satisfactory fluid intake The usual treatment of acute febrile conditions is indicated Some individuals obtain relief of sore throat with hot saline irrigations of the throat Cleanliness of the mouth should be assured, but powerful antiseptics should be avoided

In the dangerous toxic cases of scarlet fever which he saw in Paris Trousseau (ed 1869) was impressed with the therapeutic value of cold sponges for relieving cerebral symptoms and even saving life Cold applications are logical because hyperpyrexia is common in fulminant cases, and body temperatures close to 107° F are a menace to life In kittens, placed in a warm chamber for 15 to o minutes until the rectal temperature reached 107° F, Wegman (1939) found that convulsions and other cerebral symptoms occurred, and on section damage of ganglion cells was observable histologically Chemical analysis of these brains revealed an abnormal distribution of fluid between intra and extra cellular spaces (Yannet and Darrow 1938) Acetylsalicylic acid when given orally 4 to 6 times daily will help to keep the fever below dangerous levels If sodium bicarbonate is included in equal amounts, nausea and vomiting should not result

Scarlet fever is the least communicable of the exanthemata, and successful methods of isolation are based on the assumption that the infection is by contact In many situations treatment at home is satisfactory (Parsons, 1927) The technic of medical asepsis ', largely popularized by Chapin (1912), should be used in hospitals and as much as possible at home Anything which touches the patient or his discharges is considered dirty All attendants see to it that only their hands gowns and instruments become contaminated The hands are washed with soap and running water immediately after each contact, and the gowns are sterilized after each use It is almost impossible to follow even these simple measures in the home and where there are susceptible children in the household, hospitalization of the first case or segregation of the other children is indicated

In hospital practice it is easy to keep patients in bed twenty one days, and as they generally are admitted on the third or fourth day, this carries them past the time when nephritis or late adenitis is most apt to develop It is difficult to say that this measure really lessens the incidence of sequelae In general practice with children at home it seems impossible to keep them in bed three weeks So it is better to let them up earlier warmly dressed and under proper supervision

Sulfonamides

Thanks to Domagk (1935) and others sulfanilamide and other sulfonamides (see Vol IV, Chapt XXX-A of this system) have become valuable drugs in infections due to hemolytic streptococci Sulfadiazine is now the derivative of choice, since it is as active as related compounds but toxic reactions are less frequent and

fusions should be used A sulfonamide as sulfadiazine or better still penicillin, should be used

The treatment of post scarlatinal nephritis is similar to that of acute nephritis in general the giving of fluids and salts must be attended to Judgment is necessary in some cases to keep from using harmful measures The appropriate therapy is well described by Aldrich (1937) During the time that nephritis is apt to occur

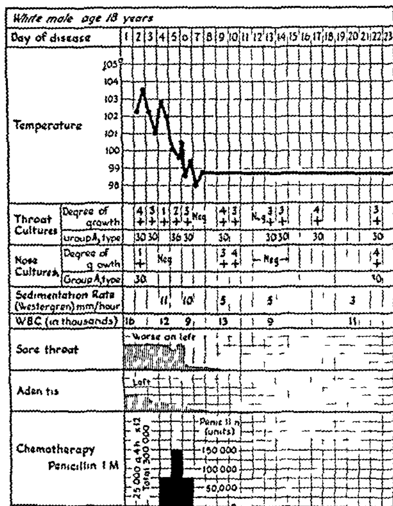


Fig 37 Effect of 300 000 units of penicillin on the clinical course of scarlet fever Rash disappeared in 48 hours Note that hemolytic streptococci reappeared in the nose and throat without relapse Cultures were taken daily

mide are sepsis involving meninges or pleurae, septicemia, cellulitis, mastoiditis otitis media, etc The value of the drug in cervical adenitis has been less clear, and no benefit has been seen in scarlatinal nephritis The drug did not lead to a critical cure in the toxic phase of mild scarlet fever and did not cause an early disappearance of the rash These experiences depend on attempting to maintain a level of 10 mgm per cent in the blood serum Hoyne and Bailey (1937) found that prontylin grs x (0 6 gm), t i d, was ineffective in eradicating the carrier state There are data suggesting sulfanilamide may be used prophylactically to protect rheumatic children against streptococcal infections (Thomas and France, 1939, Coburn and Moore, 1939) The worth of other sulfonamides, particularly sulfadiazine, in this connection has since been amply proved

Sulfonamide sickness is especially confusing in scarlet fever, which has so many complications and sequelae of its own but generally the two conditions can be differentiated, and the usefulness of sulfonamides, in appropriate cases, far outweighs their disadvantages

Penicillin

The action of penicillin in hemolytic streptoccal infections is even more striking than that of sulfonamides, and toxic reactions to it are unusual and rarely serious They consist mainly of urticaria and angioneurotic edema The total incidence of such reactions is about 3 per cent Adequate blood levels are obtained with the intramuscular administration of aqueous penicillin every 3 hours The usual total daily amount for an adult formerly was about 240 000 units and that for a child is one third to one half of this depending on weight Now much larger doses are in general use Fairly comparable blood levels follow the once daily injection of penicillin in beeswax and oil Standard preparations contain 300 000 units in 1 c c Penicillin therapy should be continued for at least one week since shorter courses may result in reappearance of the organism in rhinopharyngeal cultures and often a relapse The clinical course of two adults treated with penicillin is shown in Figs 37 and 38 (Spink Rantz and Boisvert, 1946) The oral use of penicillin although handy, produces varying blood levels In the presence of purulent complications intramuscular treatment with large doses of penicillin is clearly indicated

Treatment of Complications

In septic cases after the specific toxemia has been overcome either by the administration of antitoxin or in cases seen late in the disease, by autogenous development of antitoxin the usual methods applied to septic processes in general should be instituted In children with serious septic complications blood trans

fusions should be used A sulfonamide as sulfadiazine, or better still penicillin should be used

The treatment of post scarlatinal nephritis is similar to that of acute nephritis in general, the giving of fluids and salts must be attended to Judgment is necessary in some cases to keep from using harmful measures The appropriate therapy is well described by Aldrich (1937) During the time that nephritis is apt to occur

FIG 3 Effect of 300 000 units of penicillin on the clinical course of scarlet fever Rash disappeared in 48 hours Note that hemolytic streptococci reappeared in the nose and throat without relapse Cultures were taken daily

the urine should be examined frequently, as the presence of this condition occasionally may be detected first by observing hematuria. Most cases recover completely but death may occur in the acute attack with carditis (Goodhart 1879) or with convulsions (Blackfan and McKhann, 1931). For treatment of acute hemorrhagic nephritis see Chapt. X and Chapt. XI in Vol. III of this system.

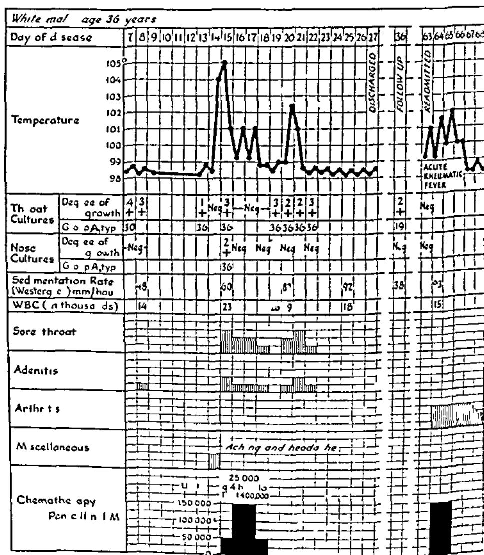


Fig. 38. Effect of penicillin on clinical course of severe tonsillitis. Note the bacteriological and clinical relapse after 400 000 units had been given. Acute rheumatic fever developed in the patient following appearance of new type of hemolytic streptococcus.

Adenitis is to be treated expectantly since frequently suppuration does not occur Aspiration of pus from an early abscess with instillation of penicillin in addition to penicillin intramuscularly will result in cure but the period of hospitalization is the same as when the abscess is allowed to progress to the stage for incision and drainage *Post scarlatinal arthritis may be relieved by splinting the* joints with cotton bandages Salicylates may be useful

Summary of Treatment

Current scarlet fever can be described as mild although severe examples are seen General supportive measures always are indicated but the usually mild case of scarlet fever requires no additional therapy if evidence of septic complications is lacking Penicillin has the advantages over sulfonamides in such cases of more prompt eradication of hemolytic streptococci and almost complete absence of significant reactions It has the discomfort associated with intramuscular administration Antitoxin should be reserved for the more toxic cases and these usually respond dramatically The appearance of the patient age complications and knowledge of the prevailing severity of scarlet fever in the community should help the physician to decide on the type or types of therapy to be employed

Period of Isolation

Special precautions should be taken when some members of the family are food handlers and particularly if handlers of milk The local board of health should arrange such matters The rules for isolation after scarlet fever vary from state to state In uncomplicated cases the period varies from one to five weeks and children with post scarlatinal sepsis are considered potentially infectious as long as the discharge persists

Nasal and pharyngeal cultures for hemolytic streptococcus in the 4th week and cultures of exudates have proved disappointing as the sole indicator of infectiousness in scarlatinal convalescents There is some promise in a method which depends on a correlation of findings Gordon (1934) uses two weeks of isolation for adults and children over 15 in the summer and fall For the rest he uses three weeks as a basic time which he prolongs according to the presence of infected discharge containing hemolytic streptococci

The problem of carriers still is unsettled In some communities there are so many carriers that a *few more or less seem unimportant In other communities* the carrier state is uncommon (Cooke 1928 a Topley and Wilson 1936) and then it might be justified to pay some attention to hemolytic streptococci in throat cultures or more particularly to positive nasal cultures Hamburger and associates (1945) from their studies on the spread of streptococcal infections in army

camps lay great stress on the importance of the presence of the organisms in the nose as contrasted with the throat

Streptococcal Fever and Streptococcosis

The clinical bacteriology and epidemiology of the various manifestations of scarlet fever show it to be but one aspect of a major disease of childhood namely, infection with hemolytic streptococci In place of this unwieldy designation Dr Daniel C Darrow of our Clinic has suggested the term streptococcal fever This name is especially appropriate for pediatric practice, where members of the group of pathogenic human hemolytic streptococci are found in all primary streptococcal disease, and where other streptococci, auch as *Streptococcus viridans*, appear merely as normal inhabitants of the alimentary tract or as bacteria, which grow in devitalized tissue or on deformed valves of the heart

Dr Grover F Powers finds the expression, Streptococcosis", convenient to explain the natural history of infections with strains of streptococci pathogenic for man 'Our attention to the similarities in the patterns of reaction of patients of different ages to tubercle bacilli and to streptococci, respectively, was focused by the late Dr Trask

From a quantitative standpoint the two diseases are similar, for although in the acute form streptococco is may seem of relatively short duration compared with tuberculosis one can hazard the guess that about as much acute illness in validism, and emotional and economic distress are involved in the one infection as in the other, especially if hemorrhagic nephritis and rheumatic fever are con sidered in association with hemolytic streptococcal disease

As regards tubercle bacilli and streptococci, there are human and animal strains of both Persons of all ages are susceptible to infections in one form or another with tuberculosis and with streptococcosis, in neither disease does one attack confer complete and permanent immunity For both diseases the portal of invasion is most frequently the respiratory tract and contagion is principally by sputum or pharyngeal oral and nasal discharges Unless milk is pasteurized or sterilized it also may be a source of infection in both diseases, milk borne tuber culosis is usually bovine in origin whereas milk borne streptococcosis — the most notable clinical form of which is septic sore throat — is usually from human sources Neither disease is highly contagious except in the intimacy of the home

However it is of more importance to direct attention to the fact that the numerous streptococcal diseases (pharyngitis tonsillitis erysipelas scarlet fever etc) are not caused as was long held each by its own special organism rather it is now clear any one of the clinical forms may result from infection with any one of the strains of the organisms pathogenic for man Our present conception is that these apparently diverse manifestations may be characterized in various

ways by reference to age of patient site of localization history of previous infection and hence stage of immunity and allergy

The paradigm of tuberculosis is suggestive also in respect to carriers of streptococci such persons have what may be designated latent streptococcosis — *they harbor streptococci in the rhinopharynx but evidence no illness* The situation seems somewhat analogous to that of a patient with latent tuberculosis in whom tubercle bacilli are harbored but the patient is not dangerous to contacts until a change in resistance leads to active disease A typhoid carrier is perhaps a better example since such a person is dangerous to others but is himself not ill At the present time we are obliged to speak in terms of latent and active streptococcosis and of sick and healthy carriers of streptococci with not too clear a conception of the clinical connotations of the words Various factors as in tuberculosis may convert latent into active cases of disease Various factors also as suggested by the work of Coburn and Pauli may influence the importance of carriers as regards communicability of streptococcal disease

In spite of the varied manifestations of infections by hemolytic streptococci scarlet fever remains the classical example

camps lay great stress on the importance of the presence of the organisms in the nose as contrasted with the throat

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September 1 1947

CHAPTER XXII

RUBELLA
(GERMAN MEASLES)

By CONRAD WESSELHOEFT

TABLE OF CONTENTS

Synonyms — English rubella German measles
French rubéole
Spanish rubéola, rubella, sarampion aleman
German Roteln Rohteln or Roetheln, Rubeolen Rubeolae
Swedish rubeola

Definition — An acute infectious disease of virus origin characterized by a macular exanthem swelling of the postcervical and postauricular lymph nodes and an ability to produce serious injury to the fetus especially when acquired during the early months of pregnancy

History

In view of the awakened interest in rubella through its deleterious influence on the fetus it is appropriate to review the historical aspect of this disease The term Roetheln or Rotheln was introduced from Germany, and this was the term under which rubella was described first in America[1] Indeed in the First Series of the Index Catalogue of the Library of the Surgeon General s Office this German term Roetheln is used as the heading According to Emminghaus[2(a)] descriptions of the disease were given by de Bergen in 175 and Orlow in 1758 but while these authors did not establish this malady as an entity, they did call attention to its manifestations These and later excellent descriptions of the disease by other German physicians and the acceptance of the German name presumably brought about the common usage of the term, German measles, introduced by Balfour[3] in 1857

English writers have made notable contributions Willan[4] in 1813 described it under the heading *rubeola sine catarrho* He considered it a spurious form of measles, but he added that "persons receiving the miasm in this form are peculiarly liable to a second attack of measles It is interesting that in April, 1814 Maton[5] presented a paper before the Royal College of Physicians in which he drew attention to this malady as a disease entity to be distinguished from scarlet fever by an incubation period approximating eighteen days by its relatively rapid course, by the pronounced occipital lymphadenopathy and by the absence of a strawberry tongue and acute angina

Others established the fact that an attack of this disease tended to afford immunity against subsequent attacks but not toward measles or scarlet fever and further, that neither measles nor scarlet fever protected against this disease Maton did not establish that rubella afforded a specific immunity as is so often stated in the literature but he did give us a clear account of the disease in the English language establishing its entity in contrast to Willan who considered it to be a modified measles

In 1940 there appeared an editorial[6] in the Edinburgh Medical and Surgical

Journal entitled "A Hundred Years Ago" in which Robert Paterson[7] is given the credit for the first description of rubella in English referring to an article by this author published in 1840. Paterson wrote that he was "unaware of any description of this disease in our language." Whereupon he cites numerous German authors on the subject and proceeds to give his own observations with several fatalities. A perusal of his case reports indicates that while Paterson at times was describing rubella he included also cases which were obviously severe forms of measles and scarlet fever. Indeed his tabular differentiation of the three diseases shows only too clearly that he shared the confusion in this respect of his European contemporaries. In spite of these observations many authorities insisted that rubella was either a modified form of measles or scarlet fever while others argued that it was a hybrid of these two diseases.

The names used for this disease in different countries have long been the cause of confusion. Thus Schonlein[8] described the disease under the heading "Exanthema hybridum" and then proceeded to give it the name of rubeola to distinguish it from morbilli or true measles. Eventually the term "rubeola" was adopted for measles. However even to this day in Sweden[9] rubeola is used to designate rubella, in Spain rubeola and in France rubeole, while as late as 1904 Pospischill[10] of Vienna used rubeolae.

This confusing terminology is important to keep in mind in discussing this disease with physicians from other than English speaking countries as well as in making any search of the literature. In 1866 Henry Veale[11] in a description of an epidemic in Bombay introduced the now generally accepted term rubella. He concludes his article with these words: "I therefore venture to propose Rubella as a substitute for Rotheln."

John Homans[1] is credited as being the first physician in the United States to describe this disease in a paper read before the Boston Society for Medical Improvement on April 14, 1845, but this paper was never printed. Cotting[12] was present at this meeting and presented a paper himself on the subject in 1853, but it was not published until 20 years later. Influenced by the writings of the 1870's by Emminghaus[2(a)] and Thomas[13] in Germany the subject was pursued in England by Murchison[14], Liveing[15], Cheadle[16] and Shuttleworth[17] and in America by numerous authors including J. Lewis Smith[18], Kingsley[19], Earle[20], Edwards[21] and Hardaway[22], culminating in the two classic papers of Atkinson[3] and Griffith[4] in 1887, the latter offering an extensive and accurate bibliography, and the work of Corlett[5] in 1902.

In this period there was a lively interest in this disease in England, America and Europe during which rubella came to be recognized as a separate entity with distinguishing characteristics. Since then, aside from a comprehensive review of the subject in 1928 by Schamberg and Kolmer[6], this disease was given scant attention up to 1940. The general attitude prevailed that rubella was of little

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Distribution and Age

Rubella occurs in many countries including North and South America Europe Asia Japan and Australia Like measles it is uncommon in the first 6 months of life However cases have been reported in the newborn[5] A case of rubella in an infant 18 days old and another case in an infant 10 weeks old were reported by Hadfield[31] At the same time Mingay[32] reported rubella in an infant 5 weeks old without pyrexia Veitch[33] also had a case in a five weeks-old infant and Freitag[34] cites a case in an infant 8 weeks old All of these cases occurred in the 1940 epidemic in England and in all of these instances the disease appears to have been mild in character

Many writers have been impressed with its frequency above the age of 14 This may be attributed to the fact that this relatively mild disease is often missed in early childhood whereas in the older age groups it is apt to attract more attention and is more likely to be referred to isolation hospitals Nevertheless one must not lose sight of the fact that epidemics do occur in institutions composed of young children[35,36] It is rarely seen in elderly people although one case said to have occurred in a woman aged 73 has been handed down through the literature for the last 60 years[2( )] A recent case reported in an epidemic in Dorset England was in woman 82 years old[37( )]

Period of Incubation

The period of incubation has been a subject of interest as well as a feature which distinguishes it from both scarlet fever and measles As already mentioned Maton[5] in 1814 was the first to establish the period as averaging 18 days Emminghaus[( )] Thomas[12] and Earle[6] confirmed this Pospischill[10] arrived at the figure of 17 days with a maximum of 21 days Many writers on the subject have been content to compile the limits as recorded in the literature copying and enlarging without due discrimination until an array of variable figures from forty-one authors without references is supplied[6] Since many of the authors cited apparently included cases of scarlet fever and measles the compilation is of little value In attempting to determine the incubation period it is necessary to take into consideration that infectivity presumably precedes the appearance of the rash This element would lengthen the period when estimated from the exposure to the onset of symptoms provided that such exposure existed prior to development of the eruption From a single three hour exposure to the onset of the eruption the period was exactly 18 days as reported by Lindberg[9] It is safe to say that the incubation period is similar to that of mumps namely an average of 18 days This figure is confirmed by a chart presented by Aycock and Ingalls[38]

consequence, and its only importance lay in being able to distinguish it from the more serious measles and scarlet fever. In 1940 Gregg's[7] recognition of the danger of rubella to the fetus in utero substantially altered this attitude. In looking back through the previous literature I can find no evidence that this danger was ever suspected. The possible danger to the fetus in the form of its actual demise with stillbirth or what is even worse, the prospect of serious congenital deformities has awakened a vigorous interest in the pathogenicity, nosology and epidemiology of rubella.

Etiology

The causative agent of rubella is a filterable virus. Thomas[13] of Leipzig in 1872 remarked that the disease was caused by a specific virus (ein bestimmtes Virus) using the term in the sense of a contagium or poisonous substance. Steinmaurer[8] in 1938 professed to have demonstrated with the fluorescent microscope the virus in smears from the nose and throat and blood as well as from the contents of cantharides provoked blisters over the rash and to have grown the virus on the chorioallantois of the egg embryo. The evidence presented is not convincing that he had isolated the virus of rubella.

Hiro and Tasaka[9] collected normal saline washings of the nasopharynx during the eruptive phase of rubella patients. A portion of this was put through a Berkefeld filter W and another portion through a Seitz filter. These filtrates were injected subcutaneously into a group of 16 non immune children convalescent from other diseases. The first portion yielded 2 cases of characteristic rubella and 2 cases of rubella without rash. The second portion yielded 2 cases with rash. The incubation period was 7 days in 3 cases and 8, 11 and 17 days in the 3 other cases. This shortened incubation period in the majority of positive results is comparable to the five day incubation period of mumps in monkeys, when the saliva filtrate is injected into the parotid ducts.

Habel[10] in 1942 used nasal washings with salt solution obtained within 12 to 24 hours after the appearance of a typical rubella rash and this filtered or unfiltered material was introduced intranasally, subcutaneously, intra peritoneally and intravenously into macacus mulatta monkeys. The monkeys proved to be equally susceptible to rubella by all four routes. However, not all the monkeys showed a rash. Washings used from cases on the third day of the disease yielded negative results. Furthermore virus was demonstrated in the blood of patients bled within 12, 24 and 30 hours after the onset of the rash but not in blood taken on the third day. Finally this author reported successful cultures of rubella virus on the chorioallantoic membrane of the developing chick embryo in 2 out of 4 attempts although no specific pathological lesions were found in the inoculated membranes or the embryo organs.

Prodromal Stage

Prodromal symptoms usually are in proportion to the severity of the subsequent eruption In the more pronounced cases in the older age groups we have found prodromal symptoms in the form of headache chilliness muscular aches and pains fever and the characteristic enlargement of lymph nodes Anorexia is met with occasionally while nausea and vomiting are very rare In children under observation in a hospital ward a slight rise in the temperature during the 24 hours preceding the eruption may be the only prodromal sign of the impending development of rubella

Blood Findings

The blood findings are of particular interest in the prodromal stage because here it is that they may give us a warning signal but on the whole they are unreliable Sometimes I have found a marked leukopenia in the prodromal stage which often changes during the eruption to a lymphocytosis along with the appearance of a few monocytes Careful blood studies by Lindberg[8] failed to yield any blood findings of diagnostic value Hynes[11] carried out serial leukocyte counts on 61 adult cases He found an absolute leukopenia as a rule at the onset which changed to an absolute lymphocytosis on the sixth day and a neutrophylic leukocytosis after 10 days These findings offered no difference from that observed in measles although they differ from the findings in scarlet fever One quarter of the cases showed an increased sedimentation rate of the blood during the first week

During my term of service at the Haynes Memorial there have been admitted 1 041 cases of rubella I myself was one of these patients It was the only disease I have acquired from my services in this contagious department Added to this number there were numerous cases which originated especially on the scarlet fever wards as a result of exposure prior to the scarlet fever and by further contamination of the ward from these cases There were no deaths and no serious complications except for 2 cases admitted with rubella encephalitis and 1 very mild encephalitis of 3 days duration which developed on the sixth day of the disease It is on the basis of this experience with the disease that this chapter is prepared

Symptomatology and Course

Exanthem

The eruptive stage is characterized by the appearance of small pale or rose pink macules which come out in the great majority of cases on the face and scalp

Period of Infectivity

Inasmuch as the virus of rubella has been recovered from the upper respiratory tract in the early stages of the disease, it would appear to be spread from this area The period of infectivity probably resembles that of measles and so may extend from several days prior to the eruption to the fading of the rash Since the catarrhal symptoms of measles predominate in the early stages in contrast to rubella, we should expect to find the infectivity rate of measles higher than that of rubella, and such is the case Geiger[39] found an attack rate of 12 per cent in school children exposed to rubella, whereas in 10 families studied the attack rate was 65 per cent Humphrey and Ekermeyer[36], on the other hand, found that during an epidemic in an institution 48 per cent of the children exposed were attacked and Michael[35] reported 80 cases among 199 children in another institution Incidentally all those under 6 contracted the disease Whether the virus of rubella is spread from the exanthem itself has not been determined although Steinmaurer [8] claims to have isolated the virus from blister fluid from the skin Thus it is that isolation, as in measles, usually is accomplished too late to control the spread Griffith [4] noted that with "prompt and careful isolation' of all cases with the appearance of the rash there were 37 children in one institution and 26 in another who contracted the disease in spite of these precautions

Isolation beyond the duration of the eruption probably is unjustified Geiger's[39] recommendation that cases should be isolated for the duration of palpable lymph nodes is untenable when one considers that the posterior auricular glands may remain swollen indefinitely Moore[10] registers a complaint from Norwich England against a 14 day isolation requirement for patients and a 21-day quarantine of contacts No such rules regarding isolation are encouraged in the United States

Immunity

An attack usually affords a lifelong immunity Late second attacks of rubella have been observed but are rare[38] However there is an interesting feature in regard to this disease which has been remarked upon by several authors namely, relapses I have seen this on several occasions In this respect it is somewhat similar to scarlet fever, although in scarlet fever relapses during convalescence are due supposedly to reinfection by other strains of streptococci Humphrey and Ekermeyer[36] report 19 relapses among 305 cases in an institution The relapse usually was milder than the original attack and occurred in the third week in 15 cases in the fourth week in 3 cases and on the forty first day after the original attack in 1 case These authors point out that the establishment of immunity often is delayed and this permits of reinfection by subsequent exposures during this period Geiger[39] reported 15 relapses In 5 individuals there were 3 distinct relapses

Conjunctivitis

In mild cases the eyes are not affected but where the rash is severe conjunctivitis is common This conjunctivitis differs from that of measles in that, while in measles the palpebral conjunctiva is primarily involved with a bluish tinge and sometimes with Koplik spots on the inner canthus in rubella the orbital conjunctiva is involved giving a suffused pink to the whites of the eyes Photophobia is extremely rare and lachrymation is absent Moreover there is never the purulent sticky discharge so commonly seen in measles

Enanthem

The appearance of the throat has been a subject of debate for almost half a century In 1898 Forchheimer[43( )] of Cincinnati presented a paper on The Enanthem of German Measles He described a rose red eruption on the velum of the palate and uvula which appears on the first day of the skin eruption as irregularly arranged rose red spots the size of large pin heads slightly elevated above the level of the mucous membrane which do not increase in circumference and are fleeting in character He states that they may be absent with the first appearance of the skin eruption but a few hours later are in evidence and then *fade away within 4 hours sometimes leaving a yellowish brown pigmentation* In the discussion of this paper Griffith[4] called attention to the transitory and variable character of the skin eruption and the possibility of similar variations in the enanthem

Since Koplik had just described the pathognomonic enanthem of measles of which Forchheimer was cognizant it is not surprising that the pure pinky rose red spots described by him became known as Forchheimer spots in distinction to Koplik spots on the buccal mucous membrane Strangely enough Forchheimer[43(b)] in another publication refers to the enanthem as small discrete dark red but not dusky papules which disappear in a short time leaving no traces behind Forchheimer is himself to blame for the confusion due to his dual descriptions With few exceptions critics have referred to Forchheimer s dark red papules and having failed to find them or having found them only rarely they remark that *Forchheimer spots are of no significance* Thereupon they describe their finding of bright red spots similar to those so clearly depicted in Forchheimer s original paper

Occasionally I have observed both types oftener the bright red ones However I cannot subscribe to the idea that even these are pathognomonic of rubella in the sense that Koplik spots are of measles *This may well be due to the* kaleidoscopic and fleeting character of the lesions of rubella and this should be kept in mind at the bedside as well as in judging the diverse observations

and then spread downward over the body. Frequently the rash does not extend to the lower extremities. However, in severe cases the macules may be visible even on the palms and plantar surfaces. Schamberg and Kolmer [6] describe a case in a nurse where the eruption began below the knees and spread upward, finally reaching the face on the third day.

In general the macules remain discrete. However, in the more severe types the macules may tend to coalesce in certain areas, especially over the lower back and the buttocks. At the Haynes Memorial Hospital many of the cases have been among college students and in 1942 over 200 cases were referred from the Merchant Marine Corps. Several of these had very pronounced rashes with macules showing in the axillae and popliteal spaces. In one of these patients the temperature reached 104° F.

Soreness and pains in the muscles similar to influenza were not infrequent in these severe cases. Bennett and Copeman[4] noted these muscle pains in 15 per cent of over 300 cases observed by them in the British Expeditionary Forces. Occasionally the spleen is palpable.

There are two outstanding characteristics of the eruption. First, it comes out rather suddenly, and as it spreads from the face and neck downward it tends to fade more rapidly than an equally severe measles or scarlet fever. Thus on the second day it may be fading from the face while it is marked on the trunk. This early fading of the rash from the face frequently causes it to be confused with scarlet fever. On the third day the rash usually has disappeared. Secondly the eruption is often kaleidoscopic in character. On the first day the face may be suffused with a brilliant generalized erythema remarked upon by Pospischill[10], after which for a brief period the rash may resemble measles invading the circumoral area. On the second day it may look more like scarlet fever, or less frequently at the outset the rash may have a scarletiniform appearance which later takes on a morbilliform character. Miliary vesiculation in the center of the macule has been reported by Griffith [4]. I have seen it once in the form of tiny vesicles on the papillae contained within the macules on the chest, shoulders and buttocks. This was in a sailor with a very pronounced rash. Actually vesiculation is so rare as always to raise a doubt as to the diagnosis of rubella. Vesiculation is sometimes seen in measles [(b) 10] and allergic eruptions and commonly, in scarlet fever.

The more severe the eruption the longer it remains. Indeed in the very severe forms of rubella the exanthem may assume a coppery tint as in scarlet fever and still be visible on the fifth day. In these cases while there may be a chilliness and a relatively high fever the patient is never as sick as with a proportionately severe case of either measles or scarlet fever. When the rash is very marked as it sometimes is a furfuraceous desquamation may take place over the face and trunk as the rash subsides.

Rubella Ecchymotica

Strom[16] reports 2 adult cases from Stockholm in which the enanthem and exanthem were of a distinctly ecchymotic character They were not acutely ill and the blood findings were normal Aside from the ecchymoses into the mucous membrane and skin there was no loss of blood hence the condition was attributable to the lowered capillary resistance The permeability of the capillary endothelium is increased in all types of inflammation [4] The character of inflammation in the acute exanthemata is dependent on the nature of the toxic material in the blood stream It is only by these outward manifestations of these toxic substances that we are enabled to diagnose the various virus exanthemata The degree of inflammation brought about is again dependent on the amount of virus present the spreading factor and the resistance offered by the capillaries Hence it is that in rubella we may have a severe rash of ecchymotic character without severe constitutional reactions

Modified Rubella

An instance is recorded by Lindberg[9] of rubella without a rash The post auricular nodes were particularly enlarged Floystrup[18] reports the case of his own son who after a definite school exposure exhibited characteristic lymphadenitis conjunctivitis vomiting and a slight fever with only a few pale macules on the cheeks lasting a few hours as the only skin manifestations The boy s younger brother on the other hand contracted a typical attack of rubella from this exposure This case of Floystrup is misleading because of the title used It is frequently quoted as rubella without a rash which it was not Habel[20] reports 2 cases of rubella without rash one of which appears to be doubtful There is every reason to believe that rubella may be so modified as to occur without a rash but it is also highly probable that cases so reported may exhibit a fleeting eruption as in Floystrup s son and so escape the observer just as authors have failed to read the details of the Floystrup boy

COMPLICATIONS

The complications of rubella are rare except in the case of early pregnancy where the fetus is seriously affected without injury to the mother except through a possible miscarriage As in other virus diseases the menstrual cycle may be disturbed in the severe types This was first pointed out by Maton[5] an observation verified at the Haynes Memorial Hospital Lindberg[9] observed *polyarthritis* in 6 cases 3 in children and 3 in adults In the children the knees and feet were involved in the adults the fingers These cases all occurred a few days after the

recorded in the literature Humphrey and Ekermeyer[36] failed to find an enanthem in any of their 305 cases

Pharyngitis was fairly common in the rubella epidemic of 1940 both in Australia and in the British Expeditionary Forces In the former there was a simultaneous epidemic of sore throat which turned out to be due to *H influenzae* In the latter (B E I) the accompanying follicular tonsillitis was remarked upon by Bennett and Copeman[42], but no cultures are reported These authors noted also soreness of the gums Todd[44] also observed soreness of the gums in her own case "as though my teeth were falling out" Marked congestion of the nose without catarrh also was reported[4]

The throat of rubella lacks the angry red or brilliant punctate enanthem of scarlet fever In healthy heavy smokers the soft palate may present a diffuse redness with enlargement of the papillae Finally a case of rubella may be associated with the remnants of a recent common cold or be concomitant with any kind of sore throat, streptococcic or otherwise Thus it is that the appearance of the throat is by no means a reliable guide in the diagnosis of rubella

The tongue sometimes may show a bright red strawberry tip similar to that seen in the very early stage of scarlet fever, but the subsequent prominence of the papillae over the entire surface, so common in scarlet fever, never is present Pospischill[10] and Lindberg[9] have discussed the tongue of rubella and express the difficulty it has sometimes presented in diagnosis I cannot share this view, because the strawberry tip is too frequent an occurrence under other conditions to be of value in the diagnosis of rubella It is seen also in measles and in healthy persons

Lymphadenitis is characteristic This is most marked in the lymph nodes over the mastoid region known as the postauricular nodes These are often so pronounced as to be not only plainly palpable but actually visible Children sometimes will exhibit very large postauricular nodes Indeed Klaatsch[45] remarks that on this symptom alone the diagnosis can be ventured in the dark In these instances the child may complain of "earache but otoscopic examination reveals perfectly normal ear drums Lindberg[9] and others have emphasized this feature On the other hand in a few cases these postauricular lymph nodes are not perceptibly affected Consequently their absence should by no means deter one from making a diagnosis of rubella The lymph nodes in the posterior cervical chain and in the suboccipital region frequently are enlarged exactly as in measles In the more severe cases a general lymphadenopathy is observed with palpable lymph nodes in the axillae and groins These swollen lymph nodes rarely are painful and rarely exhibit any marked tenderness They often appear in the prodromal stage when the postauricular swellings are very marked, and they may remain indefinitely Indeed in some individuals they may persist for several years after the attack of rubella

the paper was published The spinal fluid pressure ranged from 120 to 180 mm of water and the cell counts varied from 8 to 500 cells, averaging 91, mononuclears predominating

Owen and Greenway[58] report a temporary retrobulbar neuritis with diminished vision in the affected eye lasting 2 weeks in a case of meningoencephalitis which developed 5 days after rubella in a 20-year-old male This patient suffered for 7 days from inability to urinate and would appear to come under the head of encephalomyelitis

Revilliod and Long[9] report a case of polyneuritis in an eight year-old boy which developed 10 days after rubella There was diplopia and marked weakness of the muscles of the extremities with loss of tendon reflexes recovery was complete in a few weeks This case also properly belongs under encephalomyelitis

Benard[60] describes the case of a soldier who 8 days after the onset of rubella developed herpes zoster of the chest There were no meningeal signs yet the spinal fluid showed 12 cells This is included in several tabulations of authors as a rubella encephalitis It would appear that this was a latent encephalitis of herpes zoster such as has been observed with mump

The pathology of rubella encephalomyelitis has been described in the autopsy findings by Davison and Friedfeld[54] as perivascular infiltration in the gray and white matter of the cortical convolutions the brachium pontis the superior cerebellar peduncle the dentate nuclei the cerebellum and the brain stem In this respect the pathology does not differ from other encephalomyelitides Putnam[61] is of the opinion that vascular occlusion with thrombosis possibly is brought about in some sense of an allergic reaction associated with the establishment of immunity whereby the clotting mechanism is disturbed Another theory which is coming into vogue is that some latent encephalitic virus is activated by the rubella virus[43] In support of this contention is the rarity in the incidence of encephalomyelitis after vaccinia rubella chickenpox and measles the similarity of the symptoms encountered and the pathology found On the other hand the allergic theory advanced by Putnam is tenable on the same grounds The answer to the cause of these postinfectious encephalopathies and how capillary resistance is lowered through inflammation must await further advances in virology

Thrombocytopenic Purpura

Ten cases of purpura hemorrhagica have been reported[62, 63] The severity of the rubella attack appears to have no relation to the incidence of the subsequent thrombocytopenia Pitten s[62] case was in a nine year-old girl who never had had a previous history of bleeding Thrombopenia with prolonged bleeding time were the only blood abnormalities found Gunn s[63] case was also in a girl aged 9 who had a previous history of mild nosebleeds since the age of 5 but with no cutaneous

rash had disappeared and were accompanied by a mild fever Potter[19] mentions a polyarthritis in a woman coming on the third day after the appearance of the rash without fever and involving the knees, wrists fingers, ankles and feet Simpson[37] reported polyarthritis of a mild type in 25 out of 72 patients with rubella in Dorset, England, in 1940, and Bennett and Copeman[12] observed this complication in the same year in the British Expeditionary Forces Gregg[27(a)] states that many of the cases of rubella in the Australian epidemic of 1940 and 1941 showed rheumatic sequelae" Among approximately 180 cases in an Arkansas winter epidemic Geiger[39] reported 36 cases of arthritis In 4 of these hemolytic streptococci were recovered from badly swollen knees

Gulzow[40] reports one case of *pancreatitis* during the acute stage with a rise in the blood diastase severe diarrhea and general abdominal pain Hodges and Witney[41] report a total of 15 cases of *neuritis* following rubella, 3 of which were brachial

Encephalitis

Encephalitis is rare and usually comes on between the second and sixth day after the onset of the rash It may be manifested as a mild meningoencephalitis or as an encephalomyelitis the latter possibly resulting from a low capillary resistance such as is seen in the skin in the ecchymotic forms Thus the symptoms range all the way from headache and rigidity of the neck to convulsions coma, muscle twitching diplopia, thickness of speech, aphasia retention of urine, bulbar palsies and weakness in the extremities Merritt and Koskoff have reported 4 cases Barraclough[43] 2 cases, Davison and Friedfeld[44] 6 and Jack[45] one In 1943 Bradford[6] reported 2 cases of rubella meningoencephalitis' occurring at a British Naval Hospital Both showed a spinal fluid cell count of 20 with marked predominance of lymphocytes One made an uneventful recovery in 2 weeks and the other in 3 weeks In the same year Margolis, Wilson and Top[7] reported 14 cases of post rubella encephalomyelitis occurring in Detroit in 1942 They estimated that one case of encephalomyelitis occurred in each 6 000 cases of rubella a ratio somewhat similar to that reported in measles and chickenpox yet far removed from the incidence of encephalitis in mumps where evidence of a benign meningoencephalitis has been present in as high as 10 per cent of the cases On the other hand the incidence of encephalomyelitis in mumps is as rare as in measles chickenpox and varicella These authors do not differentiate meningoencephalitis from encephalomyelitis Six of their 14 cases were mild and showed neurological signs for only 3 days One showed symptoms for 8 days, one for 10 days and one for over 120 days Four ended fatally There were 8 severe cases Their table includes 37 additional cases culled from the literature with a combined fatality rate of 20 8 per cent Of those that died none survived over 3 days All who recovered showed no sequelae except one who was almost recovered when

measles in combination with scarlet fever gives an exceedingly high rate of suppurative otitis media[68] especially in children in marked contrast to this one per cent of these authors Consequently tonsillitis suppurative otitis media bronchitis and suppurative adenitis in the course of rubella are the results of independent secondary infections and are in no way enhanced by the rubella Hamburger's[69] experience at an Army Hospital prompted him to remark that patients recovering from rubella show the same well recognized susceptibility of measles patients to streptococcic infections His experience could well be due to the prevalence and virulence of the streptococci in the hospital wards

Differential Diagnosis

In the differential diagnosis there are only two main difficulties encountered First of all, modified measles in children without Koplik spots may present all the symptoms of a mild rubella with the same mild post-cervical adenopathy Since the eruption of modified measles may last only a day or so with little or no fever one has to rely on the circumstantial evidence of exposure to one or the other of these two diseases plus the preventive administration of gamma globulin or convalescent serum in the case of modified measles During the course of infectious mononucleosis a pinkish scattered macular eruption may appear on the trunk extremities and sparsely on the face At the onset only a few mononuclears may be found in the blood smear as in rubella However the prolonged course of the disease repeated blood smears and differential blood counts along with later results of heterophile agglutination tests will clear up the diagnosis A case of temporary complete heart block in rubella has been reported[70] The case as described appears to me to have been infectious mononucleosis

Rubella is distinguished from mild scarlet fever by the fact that the eruption appears first on the face by the characteristic lymphadenopathy which predominates behind the ears and in the occipital and postcervical chains rather than in the anterior cervical chains which accompanies the faucial streptococcosis of scarlet fever In mild scarlet fever the rash almost never appears on the face and if so only on the temples and forehead with the rough feeling of coarse sandpaper It has been mentioned already that rubella on the second day may be confused with scarlet fever if the rubella rash has disappeared from the face but inquiries regarding the first appearance of the rash may be helpful Of course a well marked angina bleeding lines in the folds of the skin the presence of miliary vesicles and a well marked strawberry tongue make the diagnosis of scarlet fever obvious It must be kept in mind that mild scarlet fever does not always exhibit desquamation but when characteristic late peeling takes place under the finger nails it means that the patient has had scarlet fever no matter how much the case looked like rubella I have been caught by this telltale evidence more than once

manifestations Here again there was thrombopenia with prolonged bleeding time, but the leukocytes rose to 13 000 with 79 per cent polymorphonuclears In both instances there was severe and protracted epistaxis with cutaneous purpuric lesions on the trunk and extremities and without palpable spleen In both cases the bleeding stopped on the sixth day, and uneventful recovery took place Gunn cites 4 other cases reported in the literature

Warren Rogliand and Potsubay[64] report 2 severe cases in soldiers, both of whom gave a negative family and past history of bleeding tendencies One followed 2 days and the other 4 days after the onset of rubella In both cases there was epistaxis bleeding from the gums and gross hematuria with palpable spleen Both showed intestinal bleeding and one a complete lack of platelets at one time and diminished platelets persisting at the end of 50 days A prolonged bleeding time of 30 minutes was present in both There were generalized petechiae over the skin Transfusions were given in both instances Complete recovery followed prolonged convalescence

Fox and Walton[65] also reported 2 cases A nine year old white girl showed signs of purpura 10 days after the onset of mild rubella There was a platelet count of 40 000 and bleeding time of over 45 minutes with purpuric spots over the entire body Recovery followed in 3 weeks A sixteen year old boy had rubella with a fever of 103° F which was subsiding On the fifth day after the onset petechiae developed rapidly spreading over the entire surface of the extremities Red blood cells appeared in the urine Recovery followed in 2 weeks The previous histories and family histories in these 2 cases were negative as to any suggestion of blood platelet dyscrasia[66]

Relation to Secondary Infection

Any concurrent infection may occur during or after rubella but this disease does not in itself predispose to other infection Florant and Fiessinger[67] report a case of streptococcal septicemia which followed 6 days after rubella From my experience with repeated epidemics of rubella on scarlet fever wards there has been no evidence that rubella during the convalescence of scarlet fever predisposed those patients to otitis media or other streptococcal infections nor fo that matter to any other infection A review of my records on 100 such cases supports this statement In 305 cases of rubella in children Humphrey and Ekermeyer[38] had 15 complicated with tonsillitis, 3 with suppurative otitis media and 2 with suppurative cervical adenitis These last 2 complications are not given in relation to the tonsillitis Presumably a concurrent streptococcus infection was responsible for all of these 3 forms of complications In another virus disease, namely measles suppurative otitis media is not at all unusual and here the cultures usually show a hemolytic streptococcus to be responsible In fact

Soon after this experience a twenty three year old primipara was admitted to the Haynes Memorial with rubella of 24 hours duration She was at the end of her third month of pregnancy Forty eight hours prior to admission she began having abdominal cramp-like pains which persisted intermittently On her sixth hospital day she had a complete spontaneous miscarriage in spite of lutein injections ordered by the obstetrician

A third example has been granted me through the courtesy of Dr C J Dunlap This patient had an attack of rubella in the second month of pregnancy At the beginning of the seventh month examination revealed the absence of fetal heart sounds Determination of the death of the fetus led to the emptying of the uterus A macerated fetus with bilateral talipes calcaneovarus was removed The mother has since been delivered of a healthy infant

Swan and Tostevin[71( )] recently have reported a miscarriage in the third month of pregnancy after an attack of rubella in the second month Autopsy showed a unilateral cataract Goar and Potts[7] describe a stillbirth at 7 months where the mother had rubella in the first month of pregnancy The twin lived but had bilateral cataracts and a congenital heart lesion Fox and Bortin[73] report a still birth with hydrocephalus in the seventh month of pregnancy following rubella in the first month However these authors also report 2 perfectly normal twins and 2 other normal babies born of mothers who contracted rubella in the second month of pregnancy 3 normal babies of mothers who contracted rubella in the third month of pregnancy one normal baby whose mother had rubella in the fourth month and 2 normal babies whose mothers contracted the disease in the seventh and ninth month Furthermore all of these normal babies were born at full term at the expected time

From the above limited evidence several conclusions may be drawn A mother who contracts rubella in the first three months of pregnancy may (1) suffer a miscarriage (2) be delivered of a premature stillborn baby with deformities (3) be delivered of a living child with serious congenital deformities or (4) go to full term and give birth to a perfectly normal child Just what the mathematical incidence of these possibilities is as yet is undetermined but the third possibility is the one which has awakened a renewed interest in rubella

The surprising thing is that a relatively mild disease such as rubella should be capable of causing miscarriage stillbirth and congenital deformities It is well known that the more serious virus disease smallpox frequently causes miscarriage and stillbirths Indeed this has been reported[74] as high as 50 and 60 per cent In a rickettsial disease relapsing fever a fetal mortality of 92 4 per cent has been recorded[75] Perhaps the relatively lower virulence of the rubella virus enables the fetus to survive more frequently but it may survive to be born a seriously deformed child

Congenital Deformities — The greatest danger presented by an attack of ru

Measles has a longer prodromal period than rubella The presence of Koplik spots and the persistent hacking cough, along with the confluent papular eruption which is bluish in contrast to the pink papules of rubella are the outstanding features of measles As mentioned above, the palpebral conjunctivitis of measles must be distinguished from the suffused pink of the orbital conjunctivitis of rubella Forchheimer[43(b)] includes influenza in his table of differentiation based on his experience with the influenza epidemic of 1892 Naturally the respiratory symptoms of influenza predominate, and the enlargement of posterior auricular nodes is absent

The rashes of the rickettsial diseases, such as typhus and Rocky Mountain spotted fever, sometimes simulate rubella, but the constitutional symptoms of these rickettsial diseases are far more severe and persistent even though no hemorrhagic lesions develop Erythema infectiosum is a very rare disease in England and America and occurs mostly in Central Europe It has a relatively short incubation period of from 5 to 10 days The eruption appears first on the face, especially on the cheeks, as a papuloerythema then on the extensor surfaces of the extremities, reaching the trunk last of all According to Rolleston and Ronaldson[74] the lesions are polymorphous sometimes morbilliform or scarlatiniform in appearance but often tend to be annular or gyrate The rash usually lasts about 10 days, and there is little or no fever and no lymphadenopathy Eosinophilia usually is present

Roseola infantum (exanthem subitum) a disease of infants is not to be confused with rubella The symptoms consist of high fever and often convulsions, over a period of 3 or 4 days with normal laboratory findings The fever drops abruptly as a rubella like eruption appears and promptly fades Slight generalized lymphadenopathy may be present but the postauricular glands are not involved

Effects of Rubella on the Course of Pregnancy

A new era in the study of rubella begins in 1941 with Gregg s[7(a)] report of 78 congenital cataracts following attacks of rubella in the early months of pregnancy This observation has been confirmed and elaborated on by others in Australia as well as in England and the United States Furthermore investigations have now extended into the entire field of the influence of this disease during pregnancy

Miscarriages and Stillbirths — An obstetrician asked me to see a primipara in the third month of pregnancy with a typical attack of rubella The attack passed off apparently in an uneventful manner Six months later Gregg's work came to my attention Communication with the obstetrician (Dr Raymond B Titus) revealed that the patient had migrated to another city soon after the attack of rubella and had there suffered a miscarriage

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The surprising thing is that a relatively mild disease such as rubella should be capable of causing miscarriage stillbirth and congenital deformities It is well known that the more serious virus disease smallpox frequently causes miscarriage and stillbirths Indeed this has been reported[74] as high as 50 and 60 per cent In a rickettsial disease relapsing fever a fetal mortality of 92 4 per cent has been recorded[7] Perhaps the relatively lower virulence of the rubella virus enables the fetus to survive more frequently but it may survive to be born a seriously deformed child

Congenital Deformities — The greatest danger presented by an attack of ru

bella early in pregnancy lies in the possibility of the mother being delivered of a living child with serious congenital deformities This was brought to light by the observations of Gregg[27( )], an ophthalmologist in Australia, who was impressed by the fact that in a large number of congenital cataracts brought to his attention there was a history during early fetal life of rubella in the mother This discovery was made during a year in which this disease was unusually prevalent So far the approach to the problem has been backward from the finding of deformities to the discovery of rubella during the pregnancy concerned In an attempt to overcome this another type of backward approach has been undertaken in the form of surveys of rubella cases in pregnant women with a view to determining the incidence of congenital deformities These surveys have yielded rather meagre material so far, being handicapped by the backward approach, which is all we can work on until a series of sufficient cases of rubella in pregnancy have been followed through from the time the diagnosis is made Such a forward approach to the problem will supply us with the true incidence of miscarriages, stillbirths and congenital deformities Until such a time we must present the available material and draw our conclusions with the full realization that this problem has yet to be subjected to a more satisfactory method of investigation

Congenital Abnormalities Following Rubella In Pregnancy

In 1941 N McAllister Gregg[27( )] presented a paper before the Ophthalmological Society of Australia in which he reported 78 cases of congenital cataract Thirteen of these were from his own practice In 68 of these cases a definite history was obtained of rubella during the pregnancies concerned with these cases The dis ease was suspected in the remaining 10 but could not be definitely established Among these 78 babies there were 44 who showed congenital heart lesions and 3 of these were proved at autopsy to have patent ductus arteriosus Many of these cases were poorly nourished and difficult to feed This startling announcement started a survey in South Australia under the direction of the National Health and Medical Research Council of Australia by Swan and his associates[71( )] This report on 61 infants covering the period from 1939 to 1942, inclusive, revealed that 49 mothers who had rubella during pregnancy, gave birth to 31 babies with congenital defects (see Table I) Among the 31 mothers who gave birth to these babies 29 had had rubella in the first three months of pregnancy All of the 25 mothers who contracted the disease in the first two months gave birth to babies with congenital defects (100 per cent) Eight mothers, who had the disease in the third month, had 4 offspring with congenital defects (50 per cent) and the 16 who had the disease after the third month, gave birth to 2 babies with congenital defects (12 per cent)

The distribution of the congenital deformities among the 31 children is of

TABLE I

RELATIONSHIP BETWEEN THE TIME OF CONTRACTION OF RUBELLA DURING PREGNANCY TO THE OCCURRENCE OF CONGENITAL DEFECTS IN INFANTS BORN SUBSEQUENTLY

Swan and Associates[71(] (Australia)

Month of Pregnancy	Number of Infants with Congenital Defects	Number of Healthy Children	Total
0 to 1	8	—	8
1 to 2	17	—	17
2 to 3	4	4	8
3 to 4	1	2	3
4 to 5	—	3	3
5 to 6	1	3	4
6 to 7	—	3	3
7 to 8	—	1	1
8 to 9	—	2	2
Total	31	18	49

interest It turned out that the predominant defect was cardiac rather than ocular There were 17 with heart lesions 14 with eye defects 7 were deaf mutes 4 showed mental retardation 1 hypospadias and 1 equinovarus The majority were underdeveloped and presented feeding problems The combinations of defects were striking Among the 17 with heart lesions there were 8 with cataract 2 with deaf mutism and 1 with buphthalmos In this report 4 cases of congenital cataract were found where the mother denied any knowledge of an exanthem during pregnancy

In a subsequent report Swan[71(t)] with another group of associates reported on an additional 10 mothers who had had rubella during pregnancy with similar results Further reports from Australia by Welch[6] Evans[77] Carruthers[78] Vickery[79] Swan and Tostevin[71(] strengthened the conviction that rubella in the early months of pregnancy was the etiological factor in the cause of these serious congenital deformities Gregg[7(] had already raised the question as to whether the virus of rubella was the sole causative agent The epidemic of rubella in Australia that appeared to be responsible was of an unusually severe type and associated with many rheumatic sequelae Swan[71(a)] had found that a severe sore throat had been prevalent also in Australia However it was found that cultures from this sore throat showed predominance of *H influenzae* and furthermore no correlation between the sore throat and the congenital defects could be established

Thus the question of symbiosis was ruled out Then the question was raised as to whether this particular epidemic was caused by a rubella virus particularly virulent to the young fetus It so happened that at this same time reports from England and the British Expeditionary Forces also described an epidemic with similar characteristics of severity and rheumatic sequelae[37( ) 42]

In a comprehensive report from New South Wales by Gregg and associates[7(b)] in 1945 these authors came to the conclusion that the virus possibly had assumed an increased virulence, but that there was no relationship between the severity of the maternal infection and the defect in the child It seemed as if the epidemic in this part of the world had been due to a virus with particularly virulent proper ties for the fetus However the reported cases from 1933 to 1943 in school children showed a substantial rise in 1936 and 1937 (1,000 and 4 683 cases respectively) and a sharp peak of 30 228 cases in 1940, during which year 116 women were known to have contracted rubella in pregnancy although the actual number is unknown To these 116 women 117 babies were born, 78 with deaf mutism 15 with deaf mutism and heart disease 4 with eye disease 4 with eye and heart dis ease, 4 with heart disease and 6 with combined deaf mutism eye and heart disease All these defects occurred in babies whose mothers contracted rubella in the first 4 months of pregnancy except for 8 cases where the time of the attack was undetermined The great majority of the defects occurred in cases where the attack was in the first 3 months There were 5 normal babies, in which the rubella attack had occurred in the third month in one, in the fourth month in one the fifth month in two and the seventh month in one They found 2 instances where the mother had had a previous history of rubella There were 4 threatened miscarriages during the rubella attacks but no miscarriages were reported Except for these threatened miscarriages there was no evidence of any harmful effects of the rubella on the mother

Welch[76] supplied another study from New South Wales covering much this same period and dealing with 47 cases of congenital deafness born in 1938 in 34 of which there was a definite history of rubella All of these cases showed islands of deafness "Islands of deafness" is a term used to denote dead areas in the organ of Corti It is analogous to dead strings on a piano keyboard The patient does not hear certain tones

Evans[77] investigated dental abnormalities among the first group of children reported on by Swan and associates[71( )] He found that in 34 babies whose mothers had rubella during pregnancy, 23 exhibited congenital dental abnorm alities In 18 cases these defects were of a major character All except 2 of these 23 infants with dental defects showed other congenital malformations In all but 2 of these cases the mother had contracted rubella in the first three months of pregnancy The most severe defects were noted in those children whose mothers contracted rubella between the sixth and ninth week of pregnancy

Carruthers[78] carefully examined 117 of the deaf mutes already mentioned in the Gregg [7(b)] report from New South Wales and gives a detailed account of the pathology in one case Vickery[79] from a pediatric point of view described the children of 20 mothers who had had rubella in the first three months of pregnancy All were partially deaf and backward in speaking Thirteen had congenital cardiac defects and 2 had cataracts

Swan and his associates[71(b)] in 1944 published a second series of twelve cases of congenital defects following rubella in pregnancy This report includes the case of an infant with congenital cataract heart disease and microcephaly in which the mother denied all knowledge of any disease during pregnancy Swan and Tostevin[71( )] recently have published a third series comprising 40 cases with elaborate protocols and 16 cases in which the mothers suffered from other infectious diseases All these investigations corroborate the original results offered by Gregg[27(a)] and constitute a severe indictment from this part of the world of the influence of rubella on the fetus during early pregnancy

From other parts of the world similar observations have been made in the literature Martin[80] investigated 85 deaf children in London born in the years 1940 and 1941 He found that rubella had been diagnosed in the first four months of pregnancy in 24 of the mothers and was probable in at least 6 others Some of these had eye defects also and in 3 the eyes and heart were affected as well Hughes[81] reported a poorly nourished baby born 2 weeks after term with a con genital cataract and enophthalmos deaf mutism a patent foramen ovale and an apparent microcephaly with retarded mental development The mother had had a mild attack of rubella in her second month of pregnancy Simpson[27(b)], also from England reported 2 cases of congenital cataracts with heart defects and one with microcephaly In one case the mother had had rubella in the second month and in the other in the third month of pregnancy

From the United States an increasing number of writers have been reporting cases of congenital defects following rubella in the mother From New York Reese[82] in 1944 was the first in this country to describe 3 cases in which the cata racts were associated with heart lesions There followed reports from Rones[83] Erickson[84] Perera[85] Greenthal[86] de Roeth and Greene[87] Albaugh[88] Adams[89] Altman and Dingmann[90] Krause[91] Prendergast[92] Guerry[93] and Goar and Potts[72] All these authors presented cases of congenital deformities following rubella It remained for Fox and Bortin[73] to attack the problem from another and a very much needed angle somewhat in the manner used by Gregg and his associates[27(b)] in their survey of New South Wales Unfortunately in both instances the in vestigations reach backward for information into material which was poorly recorded because no particular interest was attached to the rubella at the time of the attack The purpose of all these investigations has been to study the pos sible relation of rubella to existing congenital deformities Correlation appears

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TABLE II

SEVERE CONGENITAL DEFORMITIES FOUND IN LIVING CHILDREN FOLLOWING RUBELLA IN PREGNANCY

Reported from	Year of Pub lica tion	Author	Cases	Eye defects	Deafness	Heart lesions	Micro-cephaly	Dental	Pyloric stenosis	Spina bifida	Oblit of bile ducts	Mental retardation
Australia	1941	Gregg	78	6		44						
Australia	1945	Gregg et al	130	3	85	28	44					
Australia	1943	Swan et al	31	14	7	17	5					
Australia	1944	Swan et al	12	2	3	4					1	
Australia	1944	Evans						18				
Australia	1946	Swan & Tostevin	56	1	22	10	18		2	1	1	
New York	1944	Reese	3	3		1						
Pasadena Cal	1944	Erickson	11	11		9						2
Washington D C	1944	Rones	3	3								
New York	1945	Lerera	1	1		1						
Milwaukee Wis.	1945	Creerthal	2	1	1	1						1
Spokane Wash	1945	de Roetth & Greene	2	2		1	1					
England	1944	Simpson	2	2		2						
England	1945	Hughes	1	1	1	1	1					
London	1945	Martin	o†		30	3						
Los Angeles	1945	Albaugh	o	8		5	5		1			
Minneapolis	194	Adams	2			2						
Nashville Tenn	945	Cate et al	5	4		4	1					4
New York	194	Altman & Dingmann	1	1	1							
Chicago	1945	Krause	3	3		3						3
California	1946	Prendergast	4 ‡	40		2						3
Colorado	1945	Long&Danielson	6	6		6						
Richmond Va	1946	Guerry	2	2		1						1
Houston Texas	1946	Gour & Fotts	6	6								2
Massachusetts	1946	Aycock & Ingall	1									1
Australia	1945	Vickery	7	2	20	11						
Australia	1945	Welch	34		34							
			473	218	20	210	5	18	3	1	2	1

In 10 of these the diagnosis was suspected but not definitely established

† Diagnosis of rubella probable in 6

‡ Most conservative use of figures given in order to avoid reduplication in reports of 80 cases from the State

N B Inasmuch as Carruthers studies of deaf mutes were done on cases included in the series of Gregg and associates[2(b)] and the Evans studies on dental defects were done in the series of Swan and associates[2(c)] their reports summarized in the text are omitted in the column of cases to avoid reduplication

to have been substantially established What remains to be done is to establish the incidence of congenital defects following attacks of rubella during pregnancy This can be accomplished only by working forward from a substantial series of well established cases of rubella during pregnancy with follow up investigations as to the incidence of miscarriages stillbirths and congenital defects Along with this there must be equally painstaking investigations of a similar nature on other infectious diseases occurring in the course of the gravid state Needless to say this will take time I have assembled from the literature (Table II) 479 cases in which severe congenital deformities followed an attack of rubella during pregnancy, the vast majority in the first trimester This table is a bare outline of the available statistics which obviously are incomplete in detail, because the approach so often varies with the specialty of the author Furthermore many of the babies did not live long enough for deafness or mental retardation to be ascertained The most common eye defect is cataract, which occasionally is associated with microphthalmos or glaucoma and buphthalmos The heart lesion usually is a patent ductus arteriosus The dental defects consisted of marked retardation of tooth eruption, defective tooth formation in the incisal third and hypoplasia

Conte McCammon and Christie[106] determined that in Tennessee the rate of congenital anomalies in mothers who had rubella during pregnancy was ten times greater than the rate for the population at large

I have collected in Table IV the number of healthy babies reported to have been born of mothers who had rubella during pregnancy

From these tables we learn that during the past five years there have been reported 479 children with serious congenital defects during whose fetal life the mothers suffered an attack of rubella Against this imposing figure there have been reported over this same period only 48 normal children born during whose fetal life the mothers had rubella In other words over this period in every 11 children reported to be born of mothers who had rubella during pregnancy, there were 10 with serious congenital defects as against one normal child This imposing ratio of 10 to 1 needs careful scrutiny In the first place in 10 of Gregg s[7( )] original series the mothers were suspected of having had rubella, but the diagnosis was not established Here and there through other reports some doubts may be placed on the diagnosis but these few doubtful cases would not alter the ratio of 10 to 1

One feature, which stands out in these reports is that the vast majority of the cases of serious deformity followed an attack of rubella in the first 3 months of pregnancy This is shown in Table I and again in Table III which is a composite of the surveys in Australia made by Swan and associates and by Gregg and associates which do not overlap As surveys they give us a perspective of the deformed children in relation to the normal children Purposely I have confined Table III to a compilation of the Australian surveys which yield 199 seriously

TABLE IV

NORMAL BABIES FROM MOTHERS WHO HAD RUBELLA DURING PREGNANCY

Author	Month of Pregnancy									
	0–1	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	Total
Swan and associates[71(a)]			4	2	3	3	3	1	2	18
Swan and associates[71(b)]						2				2
Swan and associates[7(a)]		1		1		1				3
Gregg and associates[74(b)]	1		1	1	2		1			6
Fox and Bortin[72]		4	3	1			1		1	10
Councilman								1		1
Conte and associates[68]								1		1
Aycock and Ingalls[74]		1		1					1	3
Totals	1	6	8	6	5	6	5	3	4	44

First Trimester	15
Prendergast[70]†	4
	19
Second Trimester	17
Third Trimester	12
Total	48

* Councilman, E. personal communication

† Figure supplied by obstetricians of California in answer to a questionnaire which had to do with rubella only in the first three months of pregnancy

cult to compare these results with those from the other surveys because no seriously deformed living children are reported. On the other hand 2 came very nearly fitting into the group of seriously deformed children. One died in utero and in the other the heart defect and the hydrocephalus repaired spontaneously. Consequently it is fair to say that these two unusually fortunate escapes in a relatively small series portray a serious hazard in 2 out of the 8 pregnancies or 1 out of 4. It is true that this figure is far removed from the ratios obtained from the other surveys. Even if an attempt were made to include the Prendergast and the Fox and Bortin series in Table III the general run of the figures for the three trimesters would not be materially altered. The normal children of these two American surveys are included in Table IV giving a total of 48 which we have placed against our 479 reports of seriously deformed children from Table II with a resulting ratio of 10 to 1.

Another feature is the fact that certain organs seem to bear the brunt of the virus attack, namely the eye, ear, heart and brain. The frequency with which

TABLE III

RELATIONSHIP OF THE TIME OF CONTRACTION OF RUBELLA DURING PREGNANCY TO THE BIRTH OF DEFECTIVE AND NORMAL CHILDREN

Compilation of Australian Surveys by Swan and associates[71( ) (b) (] and Gregg and associates[27(b)]

Month of Pregnancy	Infants with Congenital Defects		Normal Children		Total
0 to 1	29		1		30
1 to 2	88		1		89
2 to 3	55		5		60
First trimester		172		7	
3 to 4	23		4		27
4 to 5	1		5		6
5 to 6	2		6		8
Second trimester		26		15	
6 to 7	—		4		4
7 to 8	1		1		2
8 to 9	—		2		2
Third trimester		1		7	
Totals		199		29	228

deformed children and 29 normal babies, an overall ratio for the 9 months of pregnancy of approximately 7 (6 86) to 1, but the ratio varies in each trimester Thus when rubella occurs in the first trimester, the ratio is 172 to 7, or 28 to 1 In the second trimester the ratio is 26 deformed babies to 15 normal babies, and in the third trimester we find only one deformed child against 7 normal babies This indicates a greatly increased vulnerability of the fetus to the virus of rubella during the first trimester

In the California survey by Prendergast[92], which deals only with the first trimester we find reports of 40 deformed children and 4 normal babies a ratio of 10 to 1 It has been suggested that the Australian strain of rubella virus may have been introduced into California because during the past 5 years there has been close communication between the west coast of America and Australia[97] The survey in Milwaukee by Fox and Bortin[73] deals with 8 cases of rubella in the first 3 months of pregnancy From these mothers 7 normal babies were born including a pair of twins There was one stillbirth at the eighth month and one "blue baby with hydrocephalus who subsequently became normal It is diffi

mumps chickenpox varicella and herpes zoster during pregnancy but no such suggestion of a syndrome predominates in these other diseases as it does in the case of rubella The subject of the influence of other infections during fetal life needs much further investigation

Other conditions besides infections may give rise to congenital malformations Hale[96] found that the absence of vitamin A in the diet of sows early in pregnancy interfered with the development of the eye in the offspring Warkany and Schraffenberger[97] have observed similar findings in rats This brings up the possibility that the activity of a virus in the fetus may interfere with the nutrition of certain organs during the critical period of their development A valuable symposium on Congenital Factors in Disease has appeared recently in the British Medical Bulletin[98]

Treatment of Rubella

Maton[5] in 1814 considered that patients with this disease needed nothing more than purgation while Paterson[7] in 1840 favored the application of leeches over the sternum and to the chin and enough wine of colchicum to induce vomiting and purging These drastic measures were done away with during the last century

Inasmuch as rubella is a relatively mild affair in the vast majority of cases no special treatment is indicated Bed rest for the febrile stage is in order but since there is often little or no fever this need not be enforced too strictly Whether strict enforcement of rest will prevent the rare complications is problematical in view of the experience with other virus diseases such as mumps where strict bed rest has been found to be futile in this respect[99] If itching is severe which is seldom calamine lotion may be applied Gargles and nose drops are quite unnecessary Constipation if present requires gentle correction Penicillin and sulfonamides are not indicated

The question arises as to whether blood plasma or convalescent serum should be administered in large doses to a pregnant woman who is attacked by rubella Small or moderate doses would be out of the question Furthermore if the fetus is susceptible by the time the diagnosis is established the virus presumably already has combined with the embryonic tissues and no amount of serum could be trusted to offset damage One would be left with the uncertainty of the mother giving birth to a child with serious malformations The mother is not injured by the virus and the use of lutein to prevent miscarriage is open to serious objection

Prevention of Rubella

Presumptive evidence is offered by Barenberg and his co workers[100] that the intramuscular injection of 50 c c of pooled serum or plasma will prevent rubella in children This method could be used in exposed children whose mothers are

combinations of these anomalies occur is striking and tends toward a characteristic syndrome

The number of normal babies born in each trimester would be expected to be related inversely to the number of deformed babies This however, is not the case and offers a conflict In Table IV we have among the 48 normal births 19 where rubella occurred in the first 3 months as against 29 where the attack of rubella was in the last 6 months, but if we break this down, we find 19 in the first trimester 17 in the second trimester and 12 in the third trimester In Table I the figures were 4 8 and 6 respectively The discrepancy might be sought in the fact that in the Prendergast series there are none recorded in the last 2 trimesters because the questionnaire was concerned only with the first trimester However on the basis of Swan's[71] figures, where there also were 4 normal births, we could expect no material change in the total normal births for each trimester We have actually more normal babies in the first trimester than in the last trimester a result which is incompatible with the increased vulnerability of the fetus in the first trimester as is so evident in the series of deformed children

The table of normal births by trimester (Table IV) of itself offers nothing to incriminate rubella during pregnancy and as such it coincides with the results in the series of Fox and Bortin[73], which is concerned largely with normal children Nevertheless the number of normal babies in relation to the number of deformed babies by trimesters as seen in Table III is so striking that one is forced to conclude that rubella during any stage of pregnancy offers a possible danger to the fetus and in the first trimester this possibility would appear to become a probability

An interesting and baffling point is raised by two infants reported by Swan and associates[1] where the attack of rubella took place within 14 days of conception" One child had a congenital heart lesion and the other a congenital heart lesion and pyloric stenosis Sweet[94] supplies the case of a woman who contracted rubella 10 days before conception the date of conception being fixed by the husband's three-day military leave This pregnancy resulted in the birth of an infant who lived only 3 months, with bilateral cataracts patent ductus arteriosus and hydrocephalus The mother has since given birth to a perfectly normal child Hall[95] reports a child born in 1942 that has bilateral cataracts complete deaf mutism and a congenital heart lesion whose mother had a sharp attack' of rubella 6 weeks before the child was conceived These 3 cases reported from Australia California and England bring up the outrageous hypothesis' that the virus of rubella might enter the unfertilized ovum If this phenomenon were possible it might supply an explanation of some of the infants born with these characteristic anomalies of rubella whose mothers were well during pregnancy

Congenital deformities in the form of heart disease pyloric stenosis deaf mutism, microcephaly and imperforate anus have been reported as following measles

tion of a dead fetus after rubella justifies emptying the uterus for the health of the mother However, while emptying the uterus is allowed in the common law under these circumstances the statutes on this whole subject vary in different States, as for example in Maine New York and Iowa

In relation to the suggestion of terminating pregnancy after an attack of rubella the Lancet[102] has brought to light a pertinent charge to a jury by Mr Justice Macnaghten in 1938 In this case he allowed that the clause in the amendment to the Offences Against the Person Act could be construed reasonably This *clause is to the effect that no person should be guilty of performing an abortion,* if the act was done in good faith for the purpose only of preserving the life of the mother' His reasonable construction of the law was that it did not mean that the operation could be done only if the mother was in immediate danger but that the surgeon in performing an abortion would be protected under this clause if in his judgment the continuation of pregnancy would mean that the patient became a physical and mental wreck The editorial goes on to say that if a woman can be assured that her child is certain to be born with some terrible deficiency it might well have the same effect Such a liberal interpretation of the law depends on the judge and the sympathetic attitude of the jury A closer interpretation of the law makes the operation a felony unless performed for the preservation of the mother s life Conviction of such a felony brings a severe penalty with fine imprisonment and the loss of license to practice

We see in all this discussion regarding rubella in pregnancy a reversal of the old idea in folklore which attributed congenital deformities to extrinsic causes The expectant mother was supposed to be awed by something she saw or experienced during pregnancy or she was the subject of a spell cast by a witch and on the suspicion of practicing this art the witch was tortured and put to death Today the pregnant mother after an attack of rubella is doomed by the strict interpretation of the law to suffer the anxiety of giving birth to a seriously deformed child because her obstetrician is refused permission to do an abortion

Two hundred and fifty years ago New England went through the horrible witchcraft trials in which every sort of calamity was attributed to witchcraft The Scripture was quoted as it is today in relation to euthanasia and in a sense the termination of pregnancy can be construed as a form of euthanasia The Scripture used in the trials for witchcraft goes back to the Mosaic Law Thou shalt not suffer a witch to live (Exodus 22 18) Jews Roman Catholics and Protestants tortured drowned hanged and burned those suspected of practicing witchcraft In the Salem cases clergymen such as Parris and Cotton Mather urged the prosecutions and Stoughton sat as the judge Two physicians sat on the jury and contributed to the torture of the victims by their cruel tests[103] but clergymen physicians lawyers and enlightened civilians denounced the proceedings and brought a halt to the barbaric cruelties imposed by the Court It was

pregnant, and large doses could be injected also into the mothers, but just how reliable such a procedure would be remains to be determined

Prevention of rubella can be accomplished by avoiding exposure Since a lifelong immunity generally is established by an attack, it would seem wise to encourage having the disease before wedlock However, we are immediately confronted by the proposition of children exposed in kindergarten or school taking home rubella to their pregnant mothers This contingency is, of course, to be avoided if possible Consequently we may say that an epidemic of rubella in a children s asylum or boarding school is advantageous but the same statement cannot be postulated for day schools, where the pupils' mothers are in the child bearing age Until a vaccine of modified rubella virus has been brought forward that will afford a permanent immunity, this involved problem will continue to beset us

Medicolegal Aspects of Abortion After Rubella

Swan and his associates[71(a)] first introduced the suggestion of the termination of pregnancy after an attack of rubella In a subsequent article by this author and his associates[71(b)] it was made clear that no legal grounds existed in Australia for such a suggestion, and that legislation to such an end might be open to abuse Albaugh[83] and Lynch[101] in America and Hughes[81] in England have urged caution in the consideration of this idea Fox and Bortin[73] arguing from the results of their own investigations in Milwaukee, see no justification for even contemplating such a procedure The negative findings in the relatively small group of healthy babies born of mothers who had rubella in the early months of pregnancy appear to be insufficient to counteract the mass of accumulated factual evidence of the deleterious influence of this disease on the fetus Consequently this idea of terminating pregnancy continues to be entertained seriously in spite of the medicolegal obstacles with which such a suggestion is confronted

It is necessary to point out that according to common law and the statutes in some States it is illegal to terminate pregnancy except to save the life of the mother After an attack of rubella the life of the mother is not endangered by a living deformed fetus Furthermore there is no assurance that congenital deformities will result always from an attack of rubella even in the early months of pregnancy Thus one is dealing with a possibility This possibility may weigh heavily on the minds of the attending physician and the parents The purpose of terminating pregnancy is to prevent the birth of a deformed infant and to allow the mother to conceive again under more auspicious circumstances The desire to accomplish this is irrelevant in the eyes of the law because from the legal point of view this idea is prompted by social reasons which are not acceptible as valid grounds for abortion A dead fetus may endanger the life of the mother and furthermore its removal does not destroy any life Consequently the determina

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estimated that in England 30 000 suffered death for suspicion of witchcraft during 150 years By rough calculation, based on the reports of the last 5 years, there could have been at least an equal number of seriously deformed children born of mothers who had rubella in pregnancy during the past 150 years in English speaking countries It took a long time to overcome this law of Moses The following quotations from the laws of England show that time and public opinion finally brought about the change

All persons invoking any evil spirit, or consulting, covenanting with, entertaining employing feeding or rewarding any evil spirit to be used in any witchcraft sorcery, charm, or enchantment should be guilty of felony without benefit of clergy, and suffer death " 1 Jac I, c 12 (1603)

No prosecution shall for the future be carried on against any person for conjuration, witchcraft, sorcery, or enchantment " 9 Geo II c 5 (1736)[104]

The last witch was burned in Spain in 1781 and in Poland in 1793, 100 years after the Salem trials[105] The following quotation from a great scholar on witchcraft is much to the point No jury, whether in a witch trial or in any other case can be more enlightened than the general run of the vicinage' [105]

I have gone into the subject of witchcraft because it has a bearing on the history of the law as it pertains to such calamities as the birth of grossly deformed children English speaking countries pride themselves today on their interpretation of matters of law as it pertains to the rights of the individual just as they pride themselves in their application of medical knowledge and skill The newer aspects of rubella in pregnancy may yet bring about further alteration in the Offenses Against the Person Law whereby abortion would be permitted The argument that such a law might be abused is as the lawyers say, irrelevent, incompetent and immaterial if mental suffering is avoided thereby and more healthy babies are achieved

The challenge to the present law regarding abortion as applied to rubella lies in the cumulated factual evidence in the reports covering the last 5 years To date the figures indicate that when a mother contracts rubella in the first 3 months of pregnancy the chances on conservative reckoning are 10 to 1 that she will give birth to a seriously deformed child While further investigations are needed to determine the accuracy of this challenge enough evidence is at hand to warrant reconsideration of the present law

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CHAPTER XXIII

SMALLPOX AND VACCINATION

By FREDERICK FULLER RUSSELL

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September 1 1947

after the practice of vaccination was well established Today we who live in Europe and America see so little of it that it is difficult for us to realize what a scourge it was before the widespread use of vaccination No man dared to count his children as his own until after they had had the disease It is only when one of our great cities has gone through an epidemic as Montreal did in 1885-6 Boston in 1900 and Detroit in 1924 that physicians and the general public learn what a frightful thing smallpox can be and so appreciate to the full the enormous value of Jennerian vaccination as a contribution to human welfare

Etiology

The modern period in the study of variola and vaccinia may properly be said to begin with the work of Guarnieri who in 1892 first described the bodies which bear his name These bodies which he named *Cytoryctes variolæ* are found in the cells of the deeper layers of the epithelium of the smallpox vesicles and of the vaccinal lesion and are stained easily with a variety of dyes They are studied most easily in vaccinal lesions of the rabbit cornea where their development may be followed from day to day Guarnieri described both nucleus and cytoplasm for his organism and stated that it multiplied both by binary fission and by sporulation he considered the body to be a protozoan organism Later Guarnieri's work in so far as it concerned these bodies was confirmed by many observers Councilman Magrath and Brinkerhoff (1904) and Calkins (1904) made extensive studies and in the main agreed with Guarnieri's interpretation of the protozoan nature of the body Indeed Calkins described a rather elaborate life cycle for the supposed protozoan All later attempts to demonstrate the protozoan nature of the bodies however were failures and the question remained in doubt until 1906 when Paschen of Hamburg restudied the Guarnieri bodies and concluded that the spores were really the elementary bodies of a virus growing in an inclusion body in a way that is common and rather characteristic of many virus diseases Goodpasture Woodruff and Buddingh (1932) Rivers (1928) Craigie and Wishart (1936 a and b) and others have confirmed the work of Paschen and today the Paschen or better the elementary bodies are regarded as the virus of variola and of vaccinia Goodpasture has suggested that they be called *Borreliota variolæ hominis*

Paschen in his original article described the bodies as sharply rounded with a diameter of 0 2 mu appearing in general like a small coccus and having dumbbell like dividing forms The next step in the study of the virus size was not made until 1932 when Elford and Andrews measured

Definition — Smallpox may be defined as an acute self limited contagious disease characterised by an eruption which beginning as papular passes through a vesicular into a pustular stage The prodromal and eruptive stages are accompanied by fever which runs a characteristic course

Synonyms — Variola small pokkes la petite vérole alastrim amaas Kafir pox cotton pox Kinderblattern Cuban itch

History

Since smallpox is an eruptive disease with so striking an exanthem that in all but the mildest cases the patient has a characteristic appearance therefore it is easier than with most diseases to trace its history through the oldest medical writings As one might expect the history of the disease before the Christian era is difficult to trace yet most medical historians believe that it existed in China for at least 300 years before Christ and in India at a still earlier period Hirsch (1883) thinks that the home of the disease was in central Asia more particularly in India as the sacred books of the Brahmin priests contain descriptions of a disease which probably was smallpox Certain temples and goddesses both in China and in India were consecrated to smallpox from the very earliest time Major Greenwood (1935) on the other hand thinks that the focus in Central Africa may be still older but as the tribes of Central Africa have no written language the history of the disease in Africa is impossible to trace yet there is no doubt that the African focus is very old Ruffer and Ferguson quoted by Osler (1925) have described a smallpox like eruption on the skin of an Egyptian mummy of the twentieth dynasty i e about 1200 to 1100 B C

As early as the sixth century the disease was epidemic in the Mediterranean basin and was distributed by the Saracens throughout that region It traveled slowly northward and reached the Netherlands about the tenth century In Great Britain it was not recognized with certainty until the sixteenth century and soon afterwards it spread to North and South America and to the whole known world Sydenham in the seventeenth century was the first to distinguish between measles and variola It did not reach the Hawaiian Islands until 1853 when a ship brought it from San Francisco and 8 per cent of the island population was carried off (Gulick 1855)

Wherever the disease was introduced it tended to become endemic and after a time as most living adults had already had the infection it became a disease of children and so remained in endemic regions until

low temperatures for years It is interesting to recall that a century ago it was the custom to preserve and to ship the virus after it had been dried on linen thread In general it may be said that the glycerinated vaccine virus soon dies if left at room temperature also that it is killed rapidly by exposure to diffuse daylight and that it is killed quickly by ultraviolet light

The wide distribution of the virus in the mammalian fetus is to be noted It is carried by the blood and the lymph stream to all parts of the body in vaccinia as well as in variola itself However ordinarily it does not produce pathological changes in the tissue which are significant except on the skin and in the brain We must consider both variola and vaccinia as generalized diseases with the virus distributed throughout the body

The method of Ohtawara (1922) serves for the isolation of the vaccine virus from the circulating blood lymph and all parts of the body The fluid or tissue to be tested for the presence of virus is injected into the testicle of non immune rabbits and if the virus be present a vaccinal orchitis results By this method exceedingly small quantities of virus may be detected Guildemeister and Heuer (1928) report the presence of the virus in the blood as early as two hours following vaccination and for as long as nine days Many authors have noted that the virus is present in the plasma but that most of it is carried by the lymphocytes This is in sharp contrast to the belief formerly held that the virus was present and multiplied only at the site of vaccination in the skin of the arm

The experimental animal for variola studies until recently has been the monkey usually the *Macaca mulatta* It was used by Copeman Councilman Brinkerhoff Tyzzer and others with satisfactory results During the past few years white mice have been used quite successfully for studies of both vaccinia and variola The embryonated egg has been used also for both forms of the virus and it is now possible to prosecute studies on the nature the resemblances and the differences between the two forms of virus with some hope of success

Experimental Variola

J B Nelson (1938) was able to infect mice through the respiratory tract with vaccine virus These animals show coryza and pneumonia but no skin lesions they are obviously ill and many die of pneumonia In the lung tissue there is extensive necrosis of the bronchial and alveolar epithelium The virus is present in blood drawn from the heart from

the virus of vaccinia by ultrafiltration through a series of finely graded collodion membranes of different porosity and determined the particle diameter 125–175 micra mu Pickels and Smadel (1938) using the methods of ultracentrifugalization to estimate the size of the Paschen bodies find them to vary between 236 and 252 millimicrons in diameter This measurement is larger than that obtained by ultrafiltration but it confirms the belief that the elementary bodies of vaccinia are among the largest of the viruses Particles of this size are not ultramicroscopic yet under suitable conditions they pass through most filters

The elementary bodies may be stained in several ways by long action of Giemsa s polychrome stain by carbolfuchsin after preliminary treatment with Loeffler s mordant for flagella or by the silver stain of Morosow Also they may be seen clearly with the dark background microscope, and this probably is the quickest way of demonstrating their presence

Unlike many viruses the virus of variola is quite resistant It does not die out when the patient dies but persists in the crusts formed over the pustules and in the pustules themselves undertakers have been infected from handling cadavers The virus persists in the sickroom particularly in the bed linen blankets and the clothing of the patient and these articles may remain infective for short periods

In the laboratory the virus is preserved easily by placing the crusts in 50 per cent glycerine and storing them in the cold at the lowest temperature possible It is this fact that has made it possible to carry out laboratory studies on the monkey usually *Macaca mulatta* The virus may be preserved in the laboratory in mouse brain kept at low temperatures Haagen (1935) showed that when the virus is injected into the brain of mice it produces a meningoencephalitis and that such infected brains may be stored at low temperature for long periods since the virus does not suffer any change or loss of virulence The virus of vaccinia may be preserved in the same way It also has been grown and preserved in the mammalian fetus and Gallagher and Woolpert (1940) have passed the virus through a long series of rabbit embryos The virus was found in the liver lungs brain skin placenta and kidney A series of twenty seven passages was made using fetal skin for subinoculation

Vaccine virus ordinarily is preserved satisfactorily for long periods by storing it at low temperatures that is below 0° C and the lower the better Even temperatures down to 100° C below zero are satisfactory Like most other viruses it may be preserved indefinitely at minus 75° C which is about the temperature reached by mixing 95 per cent alcohol with carbon dioxide ice the so called dry ice It may be dried while in the frozen state and after being sealed in normal glass it will keep at

of the papillæ is more apt to result than in the smaller lesions Even in very small lesions sometimes there is destruction of the papillæ with inevitable cicatrization After recovery the papillæ are absent or very imperfectly developed and the connective tissue beneath has the characteristics of cicatricial tissue

Epidemiology

It is true of course that smallpox commonly is conveyed from the infected person to the well by droplet infection but only within a few feet since laryngitis pharyngitis bronchitis and lobular pneumonia are a part of the disease The infection spreads directly from person to person and almost always by *means of droplet infection in the same manner* as measles and influenza and from the epidemiological point of view it is best regarded as an infection of the upper respiratory tract which soon becomes generalized and after the initial fever has passed shows a characteristic eruption on the skin of the whole body The portal of entry *into the next patient also is through the upper respiratory tract In the* past too much emphasis has been placed on the importance of the lesions on the skin as a source of contagion It is improbable that many secondary cases arise from bed ridden patients because the danger is well known and the quarantine and nursing techniques are adequate to protect the sick *room or the hospital personnel*

Most infections come from persons who are up and around and who are still in the incubation period or from those who have mild attacks Paschen (1930) states that the pocks appear first as an enanthem in the upper respiratory tract and that these pocks show enormous numbers of *elementary bodies Since the vesicles* on the mucous membranes break down early and do not go on to the formation of pustules such as we see on the skin they liberate early in the disease enormous numbers of elementary bodies which are passed off in droplets in talking coughing and in clearing the throat It is this fact which makes the end of the incubation *period and the stage of the initial fever* so important for the spread of the disease Paschen (1930) has called attention also to the fact that elementary bodies may be present in the discharges from the respiratory tract when pneumonia or bronchitis persist even after the eruption on the skin has disappeared completely and that the convalescents may at times *serve as temporary* carriers in spreading the disease A third possibility of spreading the disease is found in the abortive case one who has a pharyngitis some malaise and fever but no eruption and who is not confined to bed and is not quarantined and in fact usually not

the 2nd to the 6th day Such mice as recover are immune to reinfection

Nelson (1940) and many others have cultivated vaccine virus on the chicken embryo and found that it is quite fatal to the embryo On the other hand when the embryo is inoculated with variola virus there is little if any visible change the embryo has some protection against reinfection and also against vaccinia Nelson (1939) carried the variola virus through 85 passages on embryonated egg and after the 64th generation it could be recovered regularly from the 5th to the 7th day This strain was inactive on the skin and testes of rabbits but in monkeys gave a cutaneous eruption of short duration after an incubation period of five days Nasal insufflation of mice gave no lesions

Pathology

The best and most complete description of the pathological changes found in variola is that of Councilman 1904 The virus is carried by the blood stream and the lesions on the skin originate in the deeper layers and gradually grow outward to the surface Vesicles may be seen also on the tongue on the mucous membranes of the mouth pharynx and larynx and on the hard and soft palate At autopsy vesicles may be found in the length of the intestinal tract Such lesions may be surrounded by edema inflammatory areas and hemorrhage

The spleen is not regularly or greatly enlarged during the stage of eruption although it may be during the secondary fever particularly if there is a streptococcus septicemia The kidneys show cloudy swelling and focal necrosis but nephritis is not common The liver generally is moderately enlarged

The skin lesions have been studied by Councilman and others Smallpox lesions follow the general rule of virus infections in that there is first a hyperplasia of the invaded cells soon followed by degeneration and necrosis The scarring depends upon the amount of regeneration in the skin Councilman states A complete regeneration without cicatrization is possible when the lesions are not extensive and do not involve the entire epithelium and also when the epithelium is destroyed over a small area only the papillary bodies remaining intact When the destruction extends into the corium and the entire architectural arrangement is destroyed complete regeneration does not take place Usually this is the case in lesions more than one half centimeter in diameter the base or stalk of the lesion being one half to one third of this These large lesions rarely show intact epithelial cells below them the area to be covered by the epithelium growing from the edge is more extensive and destruction

out the classical symptoms of the disease Conybeare (1939) describes an illness in seven vaccinated contacts of a case of confluent variola They showed short febrile illnesses but without the characteristic eruption Conybeare concludes that these illnesses were variola without eruption There were no secondary cases due to them so that for one reason or another they did not spread the disease

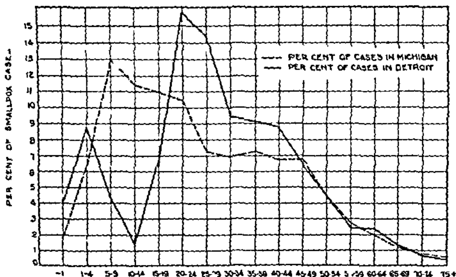


Fig 1 Smallpox cases by age groups in Detroit and in the state of Michigan exclusive of Detroit in the epidemic of 1924 Note the low rate among children in Detroit as contrasted with the rest of the state (Vaughan and others 1925 p 13)

A temporary carrier state was described by Vaughan and others 1925 which was noted in the Detroit epidemic of 1924 Persons who had been protected by recent vaccination and who did not manifest any recognizable symptoms of the disease nevertheless carried the disease during a short period from the sick with whom they had been in contact to susceptibles that is unvaccinated persons This observation serves to explain the manner in which the disease jumps to persons who have not themselves been in contact with the disease

The prevalence of smallpox in the United States during recent years cannot be shown directly since morbidity statistics are not available yet some definite information can be obtained from the mortality statistics published by the Bureau of the Census The following table (Table I) is compiled from this publication

diagnosed Vaughan refers to such abortive cases as temporary, healthy carriers

Climate as such has no influence on the spread of variola it occurs at all latitudes from the equator to the far north The season of the year on the other hand is very important and at all latitudes the disease is more prevalent during the colder months of the year and tends to disappear spontaneously during the warmer months In the temperate zones of the northern hemisphere the number of reported cases begins to increase toward the end of November continues to increase during the colder months and does not show any diminution until April and May when the number falls very rapidly to almost none during June, July, August and September

The airborne theory of infection persisted for many years but no longer is accepted in the old sense The spread of infection to the neighborhood about a smallpox hospital can be accounted for more logically by contact with hospital personnel and visitors

Neither age nor sex have any real influence on susceptibility except that infants at the breast are less susceptible than they are later after three to six months of age The disease occurs at all ages from infancy to old age The infant at the breast shows some immunity if the mother has ever had the disease or has ever been vaccinated but it passes off after the first few months of life In unvaccinated or poorly vaccinated communities it is chiefly the children who suffer In Geneva during the years from 1580 to 1760 83 per cent of the deaths were of children under five and 98 per cent were under ten years of age (Goodall and Washburn 1928) In communities where infants are vaccinated regularly most of the cases are among adults who have never been vaccinated or who have not been revaccinated since infancy The protection given by infant vaccination diminishes gradually with the years

A good example of this age distribution is shown in the monthly bulletin of the Detroit Department of Health (Vaughan and others 1925) The vaccination of infants and children had been carried out very well in the city of Detroit but had been neglected in the rest of the state The chart (Fig 1) shows that in the city the percentage of cases among persons under twenty was very low whereas the contrary was true in the state outside of Detroit The high rate in Detroit among persons from twenty to forty is explained when one realizes that huge numbers of persons from all over the United States migrated there in search of employment in the rapidly growing industries of the city and that many of these had never been vaccinated

Persons in contact with smallpox may show signs of illness but with

irregular intervals quite regardless of improved sanitation or the standard of living It is evident that its prevalence depends on one thing only and that is the number of susceptible persons in the population There are no chronic healthy carriers as in typhoid fever and tuberculosis but acute cases travel from one place in the country to another or come across our frontiers and so start new epidemics It is obvious that we can never be free from danger of an outbreak until the whole population is protected by vaccination and revaccination With this disease it is the only kind of protection which actually protects

CLINICAL COURSE

Incubation Period

The incubation period usually is eight to sixteen days but occasionally may be prolonged to twenty days Ten to twelve days is regarded as the normal period The longer incubation is not uncommon in the very mild form of smallpox which has been common in the United States since about 1896 and which often now is called *variola minor*

Initial or Invasive Stage

The initial or invasive stage of smallpox sets in abruptly usually with a chill which may be mild or quite severe The temperature begins to rise immediately and on the first day of illness may reach 103° or 104° F On the second and third day after morning remissions it may rise to 106 or even 107 F Even the cases which ultimately run a mild course may begin furiously Most of the time the skin is hot and dry but toward evening there may be intervals of profuse sweating

The pulse rate in general corresponds to the temperature and is full and rapid The respirations also are rapid and fluctuate with the temperature Prostration is extreme from the very beginning even in strong and previously healthy and powerful persons and may be accompanied by vertigo and fainting There is complete loss of appetite the lips and tongue are dry and scaly and the tongue is heavily coated The breath is offensive and this may contribute to the characteristic odor of the smallpox patient and the smallpox ward Nausea and vomiting often appear and may last until the eruption has come out In children nausea and vomiting are common convulsions frequently develop with the rise of temperature and temporary coma may follow the convulsions

Headache is almost always present from the beginning and in some

TABLE I

SMALLPOX DEATHS IN THE U S REGISTRATION AREA FROM 1900 TO 1936

Year	Deaths	Year	Deaths	Year	Deaths
1900	63	1915	81	1930	165
1901	734	1916	71	1931	93
1902	1345	1917	162	1932	38
1903	321	1918	304	1933	39
1904	176	1919	348	1934	24
1905	130	1920	498	1935	25
1906	70	1921	620	1936	35
1907	47	1922	607		
1908	58	1923	126		
1909	53	1924	871		
1910	183	1925	707		
1911	91	1926	376		
1912	124	1927	138		
1913	105	1928	129		
1914	131	1929	137		

Two periods of high mortality are shown one in 1902 and a sustained high level lasting from 1921 through 1925 Since 1931 the number of deaths has been quite small We know however from such morbidity records as are available that even during this period there has been much *variola minor* but with very few deaths

In measles it is easy to recognize certain cycles in the prevalence of that disease but this has not been true of smallpox Greenwood (1935) tells us that when the disease was first recognized in England during the sixteenth century it affected persons of all ages but by the eighteenth century it had become a disease of children just as measles is today since the adult population was immune However after the use of vaccination had become general and most children had been vaccinated either in infancy or at school age smallpox ceased to be a disease almost limited to children but attacked mainly adults who had never been vaccinated or revaccinated and whose immunity had diminished gradually or disappeared

Smallpox differs greatly in its epidemiology from typhoid fever and tuberculosis The prevalence of these two diseases has shown a steady improvement from year to year whereas smallpox comes and goes at

which the vesicle is divided make it impossible to evacuate the entire contents with a single needle puncture as in chickenpox

The papules can be felt as well as seen and sometimes it is easier to detect them by feeling than by sight They are characteristically small but hard and shot like and are obviously buried in the skin and not on

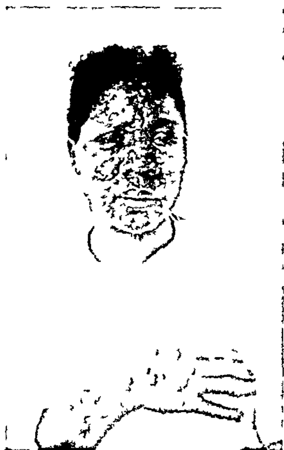


Fig 2 Smallpox eighth day Original photograph by Dr W H Mook

the surface as in chickenpox The hard shotty feeling of the submerged papule is quite characteristic of smallpox and this sign is very helpful in diagnosis

The first vesicles to appear become pustules on about the fifth day of the eruption and all the vesicles are transformed into pustules during

persons it is extremely severe Among children in addition convulsions are not uncommon and they may continue until after the eruption is well out They may be preceded and followed by coma or delirium Among adults delirium also is common during the initial fever period

Lumbar pains while not always present are nevertheless one of the most characteristic symptoms of smallpox and their presence together with chill fever nausea and vomiting suggests variola more than any of the other exanthemata The initial rash may be diffuse and suggest scarlet fever or it may be macular and suggest measles and occasionally petechiæ may be added to either of the above initial rashes At this stage it is not always easy to distinguish measles from variola and occasional cases of measles are mistaken for smallpox in the early stage in every epidemic of the latter disease According to Osler (1925) initial rashes of one sort or another scarletiniform morbelliform petechial or purpuric occur in from 10 to 15 per cent of the cases

The Eruption

The eruption of smallpox may be discrete confluent or hemorrhagic and almost always develops on the third or fourth day of the initial fever

Discrete Smallpox — In discrete smallpox the eruption begins as a macular rash although there may be for a short period an erythematous flush preceding the macular rash It first appears on the forehead and on the anterior surfaces of the wrists but within twenty four hours the eruption extends to other parts of the face and head to the extremities and to a few places on the trunk The variolous eruption unlike that of chickenpox appears mainly on those areas of the skin which are habitually exposed to the sun and air The macules are bright red in color disappear on pressure and are about two to three millimeters in diameter On the following day additional skin surfaces are involved the older macules become papules and on the third day the papules develop into vesicles which become umbilicated as they grow older The vesicles unlike those of chickenpox are multilocular and the pull of the walls of the necrotic cells is responsible for the umbilication

Councilman believes that the umbilication is due to the fact that the earliest cells involved in the vesicle formation already have undergone necrotic changes and so have lost their elasticity whereas the peripheral cells of each pustule still are capable of swelling with the increase in the quantity of exudate so that the periphery of the vesicle is raised whereas the center is not and so appears depressed The compartments into

which the vesicle is divided make it impossible to evacuate the entire contents with a single needle puncture as in chickenpox

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The first vesicles to appear become pustules on about the fifth day of the eruption and all the vesicles are transformed into pustules during

the next day or two Between the pustules the skin becomes edematous and there is an areola of inflammatory tissue about each pustule As the eruption develops the temperature drops, and by the third or fourth day of the eruption it may return to normal, but the intermission soon is followed by the secondary fever, which varies in severity with the extent and character of the eruption It is at this stage that the strepto-



FIG 3 Smallpox eighth day Original photograph by Dr W H Mook

coccus enters the picture and much of the secondary fever is due to streptococcus invasion of the pustules from the blood stream If the pustules are discrete and few in number the secondary fever may be slight or absent In such cases the secondary fever if present at all subsides after a day or two and the convalescence begins The pustules

flatten down and begin to dry and by the fourteenth or fifteenth day are cast off except on the soles of the feet and on the hands where desquamation is slower and more difficult

Confluent Smallpox — The second or confluent form of the eruption consists as the name indicates of pustules so numerous and so close together that they coalesce The distribution and character of the eruption is the same as in the discrete form of variola and because of the profuseness of the eruption and the large extent of the skin involved in the



Fig 4. Smallpox confluent ninth day Original photograph by Dr W H Mook.

inflammation the disease is more severe and the fatality very much higher The secondary fever is higher and more prolonged than in discrete variola and complications such as abscesses extensive necrosis and even gangrene are more apt to occur The eruption on the forehead and face is not only the first to appear but it is also the most extensive The pustules are more numerous then in other regions of the body and are more apt to become confluent The inflammatory reaction in the skin is striking and the edema and swelling are so extensive that the eye

lids swell the eyes are closed and the features become unrecognizable On the other hand the abdomen, the groins and the legs show fewer pustules and much less inflammatory reaction in the skin The mouth pharynx and the larynx may show numerous vesicles with more or less swelling of the mucous membrane and there may be hoarseness and difficult deglutition but the vesicles here do not go on to the pustular stage but develop into shallow ulcers which discharge great quantities of virus

The cervical lymph nodes may be enlarged in severe cases and may be quite tender The picture presented by the patient at the time of full development of confluent smallpox is indeed terrifying The pustules on the head and face coalesce break down and become an ulcerating mass upon an inflamed and swollen skin The eyes are swollen closed the features are gigantic the patient is almost unrecognizable There is high fever 103° to 105° F much thirst often delirium and sometimes diarrhea In fatal cases the temperature rises still further the pulse becomes more rapid and the patient dies about the tenth or eleventh day In the non fatal cases desiccation of the pustules and amelioration of all symptoms start on about the eleventh or twelfth day

The *period of desiccation* lasts through the third week the pustules may rupture and discharge their purulent contents or they may simply dry up forming hard crusts In the confluent cases the process of desiccation proceeds slowly and may last well into the fourth week On the face and body the crusts fall off singly but on the hands and feet the thick skin may be *desquamated* in sheets

The *pitting* which follows smallpox corresponds in general to the severity of the disease If the disease is mild and the pustules few there may be no pitting but in severe cases with thousands of pustules on a swollen and inflamed skin there is bound to be extensive pitting quite regardless of the kind of treatment used

Hemorrhagic Smallpox — The third form of the eruption *hemorrhagic variola* is the most fatal form of the disease and it occurs in two varieties (Curshmann 1875) The first is called petechial or black smallpox *purpura variolosa* The hemorrhages appear early and death follows in two to six days The second variety *variola hemorrhagica pustulosa* begins as ordinary smallpox but during the vesicular and pustular stages hemorrhages occur in the lesions both in the skin and on the mucous membranes

Purpura variolosa is not common and in children is rare most cases are among young and vigorous adults more often among males than females It is exceedingly rare among persons who have ever been vaccinated The initial symptoms chill fever backache and rash, are more

severe than in the average case particularly the fever and the initial hyperemic rash This rash is well developed in the groins and on the second or third day will show small punctiform hemorrhages Each day the rash extends and becomes more hemorrhagic and the hemorrhages increase in size Ecchymoses may be seen in the conjunctiva and on the mucous membranes The intense hyperemia and the enormous number of petechial hemorrhages change the color of the skin to a dark red hue and later to a dark plum color hence the designation black smallpox The disease is severe from the beginning and death may occur before the papules appear but more often the hard shot like papules may be seen or felt both before death and at autopsy There may be blood in the urine in the vomit and in the stools since the mucous membranes are involved in much the same way as the epidermis

Variola pustulosa hemorrhagica while extremely fatal is less so than purpura variolosa since a few cases with hemorrhage late in the course of the disease recover completely This variety of the disease while severe from the beginning does not show any hemorrhages until the eruption is well developed and the first sign is hemorrhage into the vesicles and later into the pustules As the same sort of hemorrhages occur on the mucous membranes we have hematuria hematemesis and melena in varying degrees The cases all are severe and most die on the seventh to the tenth day In general the earlier in the course of the disease the hemorrhages appear the worse the prognosis

The distinction between these two types of hemorrhagic smallpox is not always clear although the distinction holds in general but occasionally a case is mixed that is it shows some of the characteristics of each type

Leucocytosis

Leucocytosis in smallpox is well marked at the end of the first week and counts of 12 000 to 16 000 are to be expected at this time As the fever drops there may be a fall in the number of leucocytes but they increase again during the secondary fever The mononuclear elements are especially increased and this may be noted even in the mildest cases

Relation to Vaccination

Smallpox among the vaccinated may occur if the period between the vaccination and the disease is five years or more There is no sharp line between immunity induced by vaccination and susceptibility to variola

The duration of the immunity varies in different persons and there are many reasons for believing that the degree of immunity falls off gradually during a long period of twenty years or more Doering and Rosenau (1934) found that one vaccination usually protected for at least twenty years The initial symptoms chill fever and backache may be mild or severe

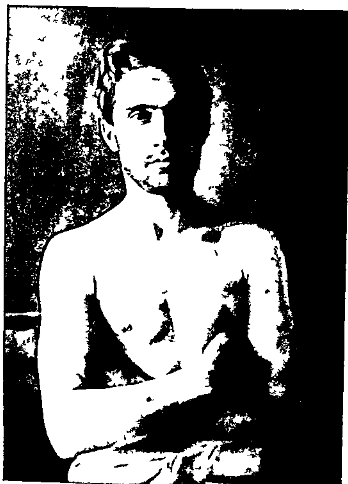


FIG 5. Mild smallpox, tenth day Original photograph by Dr W H Mook

in those previously vaccinated The initial rash rarely is present When the eruption appears it is limited in extent and the papules are few sometimes half a dozen or less Further each papule vesicle and pustule runs a shorter course than in the classical disease and if the vaccination is fairly recent the eruption not only is shortened but may be incomplete in that the pustular stage may be entirely absent. The modified

pock is smaller even as small as the head of a pin it is also more superficial and umbilification of the vesicle often is lacking Occasionally the initial fever and all symptoms may subside without being followed by any eruption whatever The fever and other symptoms disappear when the eruption comes out and usually there is no secondary fever The prognosis is good

There is the same relation between smallpox and previous vaccination as between vaccinia and revaccination After revaccination we have three types of reaction the immediate or immune reaction the accelerated or vaccinoid reaction and vaccinia proper the nature of the reaction depending on the amount of immunity remaining from the previous vaccination In the first two forms of reaction the time as well as the extent of the lesions is shortened and modified In each case the amount of immunity remaining from the previous vaccination is the determining factor

Variola Minor

A mild form of smallpox conveniently called *variola minor* has prevailed in the United States since about 1896 when the first cases were seen in Florida From this region it has spread slowly to the whole country Similar outbreaks of mild smallpox have been reported from Cuba Haiti and Jamaica and from South America particularly Brazil While many of these areas may have been infected from Florida it is not improbable that the disease came to the United States and to the other countries of the new world from Africa where a mild form of smallpox had long prevailed The disease in Africa has long been known as *amaas* or as *Kafir pox*

At first many American physicians were in doubt as to its nature but Macallum and Moody 1920 and others have shown that it is indeed true smallpox the virus being less virulent than in the classical form The serum from patients with either form of the disease fixes complement equally well and vaccination protects against both equally well

A search of the literature shows that this mild form of smallpox is not really new Cowie in Cecil s textbook of medicine remarks that Jenner recorded an epidemic in Gloucestershire which was so mild that no one paid any attention to the disease the people mingled together as usual in their ordinary occupations and no deaths occurred They called it white pox or swine pox Greenwood (1935) points out that Sydenham recognized that the mortality of variola fluctuated considerably in different epidemics and that he wrote of regular and irregular smallpox and

contrasted the mild epidemic of 1667–1669 with the severe one of 1674-1675 The same variation in the mortality rate was found on the continent of Europe in Sydenham s time

The African name of this mild variola is *amaas* or *Kafir pox*, in Brazil it is known as *alastrim* and in our own South as *cotton pox* or *Cuban itch* New names however, are not desirable It is not a new disease but merely a very mild form of variola and should be designated as such Although the mortality is very low only about ½ per cent its contagiousness is high, and it spreads even more readily than the ordinary smallpox because the patients are not ill and so continue to go about infecting others The mildness of the disease conceivably could be due to the high resistance of the host but in that case we would have both the mild and the severe forms of the disease prevailing during every epidemic That however is not the case we have epidemics of classical smallpox with 30 to 40 per cent mortality and at other times only the mild form with a mortality of ½ per cent Obviously there are at least two separate strains of the smallpox virus existing side by side at the present time throughout the world

It has been proposed some time ago in England that deaths from smallpox be reported under three heads variola major minor and unclassified This has been accepted by the committee on nomenclature of the Office International d Hygiene and is now in the international list of causes of death It is difficult to see what is gained by this step Both forms major and minor are true smallpox and the precautions to prevent spread that is vaccination and quarantine regulations are the same in each case The only difference is in the mortality and it is difficult to see that the new classification serves any useful purpose Much the same condition prevails in another virus disease yellow fever except that there we have several degrees of virulence rather than just two yet no one has proposed that we give them different names When the smallpox virus rather than vaccine virus is studied by competent persons with modern techniques it is not improbable that several strains of virus of varying virulence will be found

At the present time when smallpox is not a common disease it is possible to study the epidemiology of both forms of the disease and to trace the cases and the contacts Chapin (1934) of Providence made such a study and he states that practically all American health officers who have had experience with the two types believe that they are distinct and breed true The most important question is does the mild type ever revert to the old classical form? Many have noted the occurrence of a severe and perhaps fatal case of smallpox clearly derived

from the mild strain Rarely a second or third case develops I know of no certain record of an outbreak of the classical form derived from the mild in the United States The two strains may be present in the same locality as in Detroit in 1934 (Vaughan and associates) where investigation showed two epidemics occurring simultaneously one mild the other severe The Detroit outbreak when first recognized consisted of mild cases only but after a time cases of the classic type appeared and it proved possible to trace the latter to a patient from the northwest where the classic type was present

There is a *difference between variola minor and smallpox modified by vaccination* which is quite definite both may have a very limited number of lesions on the skin but in variola minor each lesion goes through its regular development from papule to vesicle and pustule in the normal time for each stage In smallpox modified by vaccination the individual lesions pass quickly through each stage or they may cease to develop before reaching the end of the stage of vesiculation and the pustules may be abortive or not develop at all The way the skin lesions develop serves to distinguish these two forms of smallpox the one from the other

Complications

There are many possible complications of smallpox but the most important are *bronchitis* and *bronchopneumonia* The pneumonia process may be and probably is a part of the disease and is caused by the virus itself However the lungs and bronchi may be invaded by other organisms pneumococci streptococci staphylococci and other organisms It is one of the most serious as well as most frequent of the complications *Laryngitis* is not unusual due to the presence of pocks in and about the larynx There may even be edema of the larynx ulcerations and perichondritis and necrosis of the larynx

More or less *conjunctivitis* is common even when there are no pocks on the conjunctiva or cornea itself Should pocks form on the cornea there is great danger of ulceration and rupture of the eye ball Prompt treatment with cold compresses often will control the ulceration and the eye will heal with more or less opacity of the cornea Serious eye involvement is much less common today than formerly since modern treatment is quite successful

Boils and *abscesses* are common and *bed sores* form easily and must be watched for *Parotitis* sometimes is found as in other severe illnesses *Albuminuria* is common during the febrile period but is not often fol

contrasted the mild epidemic of 1667–1669 with the severe one of 1674–1675 The same variation in the mortality rate was found on the continent of Europe in Sydenham s time

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neck scalp and on the wrists on the back more than the chest and on the abdomen least of all the distal parts of the arms and legs rather than the proximal Although the eruption may be sparse always it is distributed widely over the body and an eruption sharply limited to one area cannot possibly be smallpox

In the first days of the disease it is not always easy to distinguish between variola and varicella and smallpox should always be borne in mind if that disease is prevalent in case of doubt the Health Department should be called upon for help in establishing the proper diagnosis The difficulty is greatest when *variola minor* is prevalent There are certain general principles to guide us The eruption of varicella appears usually in the first twenty four hours of illness and is located mainly on the trunk and face and scalp and it is rare on the arms and legs In variola the eruption first appears on the third or fourth day of illness and is mainly on the face and wrists and is more profuse on the limbs than on the body if the eruption is present on the hands and feet the disease probably is smallpox In varicella the lesions come out in successive crops for three to five days and so there are seen pocks in all stages of development in the same area This is never true of variola where there is only one crop of lesions in any given area all the lesions being of the same age The varicella pocks are superficial and seem to be on the skin rather than in it they are unilocular and soft easily ruptured and break down completely on a single needle puncture In variola the lesions are deep seated shotty and multilocular and are not completely evacuated by a single needle puncture In case of doubt it is best to consider the case as variola and to make a provisional report to the Health Department In any case the patient should be quarantined and all contacts should be vaccinated If the patient has been vaccinated within five years the chances are against the disease being smallpox

Laboratory Methods of Diagnosis

Although the clinical diagnosis of smallpox by experts usually is not difficult there are always some cases where it is not easy particularly in the mild form of the disease variola minor or in cases in which little or no eruption is seen There are several laboratory methods which may be used to aid in the diagnosis

The elementary bodies may be collected from the exudate of vesicles or young pustules into capillary tubes and examined under the dark field microscope or with the ordinary microscope after staining Or an attempt may be made to isolate the virus by the inoculation of macacus

lowed by nephritis *Encephalitis* occurs rarely as it does in other acute infectious diseases

Prognosis

The mortality of the disease averages high in *variola major* 30 to 50 per cent and low in *variola minor* less than 1 per cent and if both forms of the disease are not occurring at the same time and place it is not difficult to estimate the probable mortality

Among the unvaccinated the mortality is high among children up to five years of age and may be 40 or 50 per cent It is lowest from ten to fifteen years of age After the age of fifteen the mortality increases gradually with advancing age

Among the vaccinated the mortality always is low and most of the deaths which occur are among those who have not been vaccinated within twenty years

Where the initial fever is mild, the prognosis ordinarily is good but when the onset is furious the outlook is poor although a severe initial state may be followed by a mild eruptive stage and little or no secondary fever The mortality in the hemorrhagic form always is high and this is true also of the confluent form Most of the recoveries occur among those with a discrete eruption This is well shown in an epidemic in Minneapolis reported by Sweitzer and Ikeda (1927) Among 225 cases of the discrete type 14 died a death rate of 6 per cent Among 151 confluent cases 68 deaths occurred, a mortality rate of 45 per cent Among 144 hemorrhagic cases 113 died a rate of 78 per cent Among 51 cases of purpura variolosa none recovered a death rate of 100 per cent

Diagnosis

Smallpox often is confused with other diseases in the early stages before the characteristic eruption has had time to appear During the first few days of the initial fever it may be confused with lumbago, with influenza or any other acute infectious disease If there is an initial rash the disease may be mistaken for measles although there are no Koplik spots or for scarlet fever rubella typhoid typhus or some cutaneous erythema The diagnosis at this stage is not easy but during an epidemic the patient should be isolated until it is clear that the disease is not smallpox

During the early eruptive stage the distribution of the eruption is most important In smallpox the eruption is well marked on the face

mentary bodies when they were washed clean of all tissue fragments and suspended in normal salt solution The test of course can be used only after the patient has recovered as it depends upon the presence of anti viral bodies in the blood serum Complement fixation and precipitin tests can be used also under the same circumstances

TREATMENT

Since there is always danger of bronchitis and bronchopneumonia the smallpox patient should be placed in a warm well ventilated room The initial fever is of short duration and may be controlled by frequent sponge baths with tepid water or a cold pack may be used which also helps to control the restlessness and delirium

After the eruption appears baths should be given night and morning with warm water and soap and they should be continued until convales cence is complete After the bath lesions on the skin may be painted with tincture of iodine or a dusting powder such as talcum may be used or both iodine and talcum or other dusting powder may be applied When the pocks are painful as on the hands feet and face they may be softened up with boric acid wet packs Local applications of glycerine and water or solutions of the phenols help to control the secondary in vaders and make the patient more comfortable although neither glyc erine nor phenol are good antiviral agents

Restlessness and delirium both are controlled with wet packs or better still with the continuous warm bath in which the patient may be left for hours or days The delirious patient must of course be watched at all times to prevent his getting out of bed or even leaving the hospital while delirious as has happened sometimes

The diet should of course be fluid and easily digested at first but should be increased as soon as the patient s condition permits If dys phagia is marked because of the eruption on the mucous surfaces he may have to be fed for a time by rectum

The treatment of the common conjunctivitis is important since in the past smallpox was one of the common causes of blindness The con junctiva must be cleaned frequently with weak solutions of boric acid and the margins of the eyelids be protected with vaseline in order to pre vent their becoming pasted together with the dried exudate If the cornea itself is involved the condition is serious and the expert services of an eye specialist will be needed Ice cold compresses frequently changed may arrest the progress of the inflammation

The red light treatment recommended by Finsen has not proven to be

monkeys with the contents of vesicles or pustules After a few days the animals are killed and the cells of the papules or vesicles are examined for the characteristic cell inclusions, which were described first by Guarnieri

Paul in 1916 collected the exudate from vesicles on slides and in the laboratory dissolved the dried exudate in normal saline and inoculated the scarified cornea of a rabbit with the dissolved exudate The animal is killed after two or three days and the affected eye enucleated and immersed in sublimate alcohol two parts of a saturated aqueous solution of mercuric chloride and one part of 95 per cent alcohol After a few minutes the eye is transferred to 70 per cent alcohol after which it may be examined against a dark background with a hand lens If the test is positive minute white opaque elevations are seen on the cornea The diagnosis may be confirmed by the histological examination of sections from the cornea which will show the characteristic cellular hyperplasia of the vesicle and pustule and in addition will show the characteristic cell inclusions known as the Guarnieri bodies When positive the test is of course helpful, but negative results do not exclude smallpox Varicella always is negative in this test

Coffey (1940) inoculated vaccinated and normal rabbits intradermally with material from smallpox and chickenpox and found that the lesions induced in unvaccinated rabbits were distinctive in appearance and differed from those induced by material from cases of varicella The reactions in vaccinated animals in her hands were difficult to interpret and were of only limited value The material to be tested was suspended in half a cubic centimeter of normal saline and of this about 0 2 c c was injected intradermally into each rabbit The animals were examined daily for a week Significant lesions usually were visible on the third or fourth day Another method of differentiation between variola and varicella has been proposed by Irons and his associates (1941) who draw the following conclusions Materials derived from four cases of suspected variola when inoculated on chorio allantoic membrane of ten to fourteen day old chicken embryos produce characteristic readily recognizable pocks within forty eight to seventy two hours Stained smears prepared from membranal lesions reveal moderate numbers of elementary bodies The histological and cytological changes which occurred in the infected membranes were characteristic of smallpox lesions The inoculation of chorio allantoic membranes with material from several cases of probable varicella consistently failed to give characteristic lesions

The flocculation test was used first by Ledingham (1931) who showed that the serum of convalescents would flocculate or agglutinate the el

Return cases such as we see in scarlet fever do not occur since the patient recovers completely and does not become a temporary or chronic carrier A possible exception to this is found in the patient who has a variolous bronchitis or pneumonia and who shows elementary bodies in his expectoration It will be safest to continue isolation of such cases until the pulmonary lesions have cleared up or until it can be shown by sputum studies that they are due to some organism other than the virus of variola

All smallpox cases are placed in strict isolation from the beginning of the illness As the diagnosis often is difficult in the first stage one must act upon suspicion in times of epidemic outbreaks and keep the suspected case in isolation until it is quite certain that the diagnosis is not variola Since strict quarantine is difficult to carry out at home it is much better to transfer all cases to the proper hospital where all the quarantine methods in use are well established After the patient has been removed to the hospital one can quarantine the vaccinated contacts more satisfactorily since the date of the last exposure is known definitely It is customary to quarantine smallpox contacts for sixteen days from the last exposure or until after full development of the vaccination if it has been carried out the first day after exposure Vaccination or revaccination will ward off or greatly modify an attack in a person who has been exposed if performed during the first three days after exposure Even if delayed until the fourth fifth or sixth day it may modify the severity of the attack

All persons in the household or all persons in the building if it be a multifamily building should be vaccinated or revaccinated If they still possess some immunity from a previous vaccination they will show either an immune or an accelerated reaction which produces only a trifling amount of discomfort but which will insure full protective immunity Not only should all persons who live in the house be vaccinated but also those who have entered the house during the preceding two weeks for either work or for social reasons regardless of whether they have been in direct contact with the patient or not It is much safer to rely on the protection given by vaccination than to depend upon the quarantine of the patient

Thorough disinfection either by antiseptics by boiling water or by steam under pressure of all bed and body linen and of everything used in the sick room should be carried out After the patient has been removed from the house the sick room itself should be washed down with strong antiseptics and then after airing for several days be refinished with fresh paper and paint

of any value Treatment with immune serum prepared from calves has been used but without effect, which is what one would expect None of the viruses which are all intracellular bodies are affected by therapeutic serum although antiviral sera may be used prophylactically with some success before the virus has lodged in the cells However in the case of smallpox active immunity produced by vaccination is infinitely to be preferred

Sulfanilamide has been used by McCammon (1939) with promising results He reports upon 7 patients in one family 3 had symptomatic treatment only and all 3 showed the typical eruption Four were treated with sulfanilamide and these had an evanescent macular eruption and in only one did the eruption go on to pustulization and there were only three pocks The duration of the disease, he states, was shortened by a full week and was much milder than in the untreated cases King and Rosario (1938) report one patient treated with prontosil in whom the disease was greatly modified and the secondary fever absent It is evident that the use of the sulfanilamide group of drugs in variola deserves further investigation

Immunity

Second attacks occur although they are rare and even third attacks have been described For some reason the immunity following variola is not so solid and permanent as for example in mumps measles or yellow fever

The permanent immunity following many virus diseases is believed by most investigators to be due to the persistence somewhere in the body of a minute focus of the virus which continues to act as an antigen and so leads to the production of antibodies which protect against reinfection If the virus in this latent focus dies there is no further production of antibody and the person again becomes susceptible to infection Thus we have an analogy with syphilis and malaria where we have the so called immunity of infection When the original disease germs or viruses die out the immunity vanishes

Control Measures

Quarantine

The convalescent does not transmit the disease after all the scabs have fallen off or have been removed from the thick skin of the palms of the hands or the soles of the feet where they are shed very slowly

and note that it was always contagious but usually quite mild it is interesting to assume that when virus of low virulence was used that is virus from mild smallpox the results were quite satisfactory and on the contrary that when a highly virulent strain of variola virus was used to inoculate the results were disastrous There are many reasons for believing that the two strains variola major and minor each breed true and do not fluctuate in virulence

The final period in the history of variolization as inoculation came to be called is summarized quite briefly by Garrison (1913) as follows

In 1721 Boylston began to inoculate in Boston Mass and by 1752 had 2 124 inoculations with 30 deaths while in Charleston S C Kirkpatrick had inoculated between 800 and 1000 in 1743 with only 8 deaths By 1728 there had been 897 inoculations in England and Scotland with 17 deaths In 1760 Robert and Daniel Sutton introduced inoculation by puncture with dietetic preparation and had some 30 000 cases with about 4 per cent mortality while in Paris Angelo Gatti of Pisa was given permission to inoculate by the scientific method of preparatory treatment and puncture inoculations in 1769 Prior to this the great danger of inoculation had been the large amount of virus used and the extensive sores which tended to make the patient a veritable smallpox carrier The success of the Suttons and of Gatti was such that in 1768 at the instance of Voltaire Catherine of Russia permitted herself and the Grand Duke Paul to be inoculated by Dimsdale and in the same year Ingen Housz inoculated three of the imperial family of Austria after preliminary experiments upon 200 children of the Viennese suburbs In 1770 George Motherby was inoculating in Koenigsberg but by 1774 Benjamin Jesty had performed his first vaccination The subsequent success of Jenner s experiments soon swept inoculation from the field although it had well nigh attained the status of a modern preventive injection

Vaccination

Since 1798 we have had a method of preventing smallpox and the question is a natural one why have we not prevented it? At first one might say for the first century there were a number of good excuses the procedure was far in advance of its time as the scientific basis of medicine was only beginning to appear The nature of cowpox was misinterpreted it was ordinarily considered a separate disease the occurrence of which as a mere coincidence happened to prevent variola We now know that cowpox is smallpox in the cow contracted from the milker with smallpox Further and probably most important was that vaccination during much

Inoculation

The custom of inoculation for smallpox was introduced into Europe from the East in the beginning of the eighteenth century In the Orient inoculation had been practiced for many centuries but without careful observation and controls It had two practical disadvantages one that it sometimes produced a fatal attack of true smallpox and second that it was contagious and the inoculated person could start an epidemic However even with these disadvantages it was better than the true smallpox contracted in the usual way

Before the days of Jenner and vaccination there was no form of protection other than inoculation available It was against this background of inoculation that Jenner worked to substitute cowpox or smallpox of the cow for inoculated smallpox of the human being which was sometimes fatal and always contagious

Before the days of vaccination smallpox was a common disease in Boston for example from 1649 to 1792 a period of 143 years there occurred eleven distinct epidemics at an average interval of 13 years the extreme intervals between outbreaks were 4 and 19 years

In 1776 there was an epidemic around Boston involving both the continental army and the British It is of interest to learn that in January 1777 General Washington wrote to Dr Shippen then the medical director of the American Forces as follows Finding the smallpox to be spreading much and fearing that no precautions can prevent it from running through the whole of our army I have determined that the troops shall be inoculated The expedient may be attended with some inconvenience and some disadvantages but yet I trust that its consequences will have the most happy effects Necessity not only authorizes but seems to require this measure for should the disorder infect the army in the natural way and rage with its usual virulence we should have more to dread from it than from the sword of the enemy I would fain hope that in a short space of time we shall have an army not subject to this the greatest of all calamities that can befall it when taken in the natural way

In a few months Washington was in command of a smallpox free army with his anxiety on this point entirely removed The mortality at that period exceeded 16 per cent of those attacked with smallpox Washington s army increased in size since recruits were more willing to join the forces and improved in health from that time on and ultimately he was able to overthrow Cornwallis at Yorktown (Thursfield 1940)

As we now look back over the period when inoculation was used

disease may be introduced at any time by travelers from some backward region where smallpox still is present

The best time for the primary vaccination of infants is before dentition begins and after the passive protection from the mother has worn off say during the middle part of the first year of life The best time of the year for vaccination is during the cooler months of the year We know that smallpox is a disease of the cold months of the year we also know that vaccine is prepared not during the summer but during the colder months It is logical to conclude that the best time for vaccination especially primary vaccination is not during July and August just before the school opens in the fall but during the colder months of the year This would mean that the health department clinics for vaccination of children about to enter school preferably should be held in the early spring rather than during the late summer

The best age for primary vaccination is undoubtedly during the first year of life and in Europe this is almost the universal custom It is also the law in some of our own states but in many no special attempt is made to vaccinate until just before the child goes to school For several reasons this is not the best plan The experience with post vaccinal encephalitis shows that the disease is almost unknown following primary vaccination done during infancy and that most of the cases particularly in Holland occurred when primary vaccination was carried out at school age When vaccination is performed in infancy the child is revaccinated when he first goes to school and is there first exposed to many other children and adults At this time the results of revaccination will be an accelerated reaction which will give the child very little trouble and which will step up his immunity to a good and effective level This will give enough protection to last under ordinary conditions for a lifetime but it is wise for everyone to be revaccinated on exposure or during the prevalence of an epidemic as under such circumstances one wishes the maximum immunity obtainable and we know that the immunity following vaccination diminishes gradually with the years

The Technique of Vaccination — In 1927 Leake of the U S Public Health Service described a method which is known as the *multiple pressure* method which he says has been used more or less since the early days of vaccination Leake has restudied and modified the method and strongly recommends it and in fact it is now the simplest and the commonest method in use in the United States It is sometimes called the multiple puncture method but this is quite misleading since there is no puncture or tattooing used The skin is cleaned with soap and water and then is dried after the application of alcohol or acetone A small drop of

of the period was done from arm to arm This meant that the seed virus must be selected carefully it must have neither too much nor too little virulence and it must be on hand at all time in any quantity that might be needed This was an exceedingly difficult problem and as long as humanized vaccine was used, it could not be solved

When vaccine from the calf became regularly available the whole situation changed The strain of virus could be selected carefully and be propagated to any desired extent It could be freed of most bacteria by the addition of glycerine and its preservation at low temperatures enabled one to accumulate large quantities to be used in an emergency (Copeman, 1899) In the early years of arm to arm vaccination it is astonishing how few persons actually were vaccinated in fact not enough to make very much difference in the spread of the disease The humanized virus was expensive only small quantities were available and the quality was anything but uniform All this changed toward the end of the century and we now have available a potent cheap vaccine in unlimited quantity

We have always had antivaccinationists and probably always shall, but their number is insignificant their opposition is less effective than it was formerly, and their activities no longer are a good excuse for our failure to vaccinate our communities

The most probable reason for the continued presence of smallpox either mild or classical is the failure of the medical and public health professions to understand the epidemiological situation and to take the matter of smallpox seriously If physicians and health departments were sufficiently alert and interested in the prevention of smallpox both mild and severe they could do much more than they now do to protect the population by vaccination If the general practitioner and the pediatrician do not see that all infants are vaccinated the health department should carry out the vaccinations itself

Our population in general and our own community in particular is more or less stabilized that is it neither increases nor diminishes in size and the age grouping shifts slowly so that more and more members of it belong to the older age groups and there are fewer children and young adults Yet this apparent stability is of no help to us in the matter of vaccination The community has been compared to a parade slowly and steadily marching past The older members die off each year and are replaced more or less by the children born the same year and each year everyone grows older In order therefore to maintain an immune population all the newcomers must be vaccinated in infancy and be revaccinated at school age And this must go on year after year since the

red swollen epidermis which may be quite extensive It is this stage that Jenner compared with a pearl lying upon a rose leaf a very apt comparison At the end of the third period of three days the pustule is well formed the content no longer is clear as in the vesicle but is frankly purulent By the end of the fourth period of three days the pustule has reached its full development and then begins to subside The swelling decreases the surface becomes flattened from this time on the pustule continually regresses partly by evaporation and partly by absorption and at the end of the three weeks the scab is ready to drop off leaving a bright red scar which shows more or less pitting As time goes on the scar turns white and becomes less conspicuous When the multiple pressure method of vaccination is used and the area vaccinated is not more than an eighth of an inch in diameter the scar is quite small and in after years is not always easy to identify as a vaccination This however is not really a disadvantage for a scar in itself does not give very much information about the amount of immunity remaining that can only be learned by revaccination The older methods of vaccination particularly the cross hatching and the former habit of using shields of one form or another all tended to introduce secondary infection with more or less destruction of tissue and occasionally large and disfiguring scars With the methods used at the present time such results are almost unknown as they are never due to the vaccine itself but to secondary invaders The course of the primary vaccination among infants is extremely mild older children and adults have more or less malaise headache backache some fever and perhaps loss of appetite or even nausea and vomiting These symptoms appear about the end of the week and soon disappear The regional lymph nodes usually are swollen and tender as one would expect since the vaccine bodies continue to multiply in the nodes

Re-accination — Since the immunity from vaccination diminishes gradually with age it is necessary to revaccinate at school age and again whenever there is any possible exposure to smallpox Students going to college army and navy recruits and travelers to backward regions should be revaccinated because contacts with the public are greatly increased and because an attack of smallpox no matter how mild would cause much loss of time to the patient and great inconvenience to the community The reactions following revaccination are modified by the fact of primary vaccination and in general are grouped in three classes the immediate or immune reaction the vaccinoid or accelerated reaction and the full development of the process which is called vaccinia

The nature of the reaction is determined by the amount of immunity

vaccine is placed on the dry skin in the region of the insertion of the deltoid muscle and then with a sterile sewing needle held parallel to the surface of the skin but at a tangent to the curve of the arm a number of downward pressures are made ten in primary and twenty to thirty in revaccinations in an area not over one eighth of an inch in diameter Each time the point of the needle is lifted it raises a few epithelial cells and inoculates them The vaccine remaining on the skin is wiped off with dry sterile gauze and the patient is permitted to go The scrubbing and drying should be done gently otherwise the virus may take root over the entire scrubbed area and produce an undesirably large lesion No dressing of any kind is used The vaccination runs a more normal course if it is kept dry Later if the scab falls off early and there is an exudate a piece of gauze can be pinned to the inside of the sleeve to protect the clothing In this way the vaccination is continuously exposed to the air and is kept dry There is a further advantage in this method in that the scar is small and after a time becomes quite inconspicuous The old belief that the amount of immunity depended on the number and extent of the scars has been shown to have little foundation

Vaccine virus is essentially a suspension of elementary bodies in a mixture of epithelial cells and exudate The elementary bodies are fairly resistant as viruses go but they can be inactivated easily by heat In the vaccine establishments the vaccine is stored at a temperature well below 0° C the lower the better When the vaccine is dispensed for use a very special effort must be made to keep it cold The temperature of the ordinary ice box is not less than about 45° F and this is not cold enough for long storage of smallpox vaccine It should be kept in contact with the ice or in the freezing compartment of a mechanical refrigerator it will not freeze since the original pulp has been diluted with several parts of glycerine Probably the commonest cause of failure in vaccination is due to the use of inert virus

Primary Vaccination —The primary vaccination runs a characteristic course lasting from beginning to end for about three weeks and the first part of this period may be divided conveniently into about four periods of three days each First the period of incubation and this ends in the papule at the site of vaccination This is a small rather hard red swelling in the superficial layers of the skin By the end of the second period of three days a vesicle has developed from the papule This also is superficial and raised it is usually round and shows a depressed center the so called umbilification and the content of the vesicle is clear lymph The vesicle like the eruption of smallpox is multilocular When the vesicle reaches maturity it is surrounded by an areola of

red swollen epidermis which may be quite extensive It is this stage that Jenner compared with a pearl lying upon a rose leaf a very apt comparison At the end of the third period of three days the pustule is well formed the content no longer is clear as in the vesicle but is frankly purulent By the end of the fourth period of three days the pustule has reached its full development and then begins to subside The swelling decreases the surface becomes flattened from this time on the pustule continually regresses partly by evaporation and partly by absorption and at the end of the three weeks the scab is ready to drop off leaving a bright red scar which shows more or less pitting As time goes on the scar turns white and becomes less conspicuous When the multiple pressure method of vaccination is used and the area vaccinated is not more than an eighth of an inch in diameter the scar is quite small and in after years is not always easy to identify as a vaccination This however is not really a disadvantage for a scar in itself does not give very much information about the amount of immunity remaining that can only be learned by revaccination The older methods of vaccination particularly the cross-hatching and the former habit of using shields of one form or another all tended to introduce secondary infection with more or less destruction of tissue and occasionally large and disfiguring scars With the methods used at the present time such results are almost unknown as they are never due to the vaccine itself but to secondary invaders The course of the primary vaccination among infants is extremely mild older children and adults have more or less malaise headache backache some fever and perhaps loss of appetite or even nausea and vomiting These symptoms appear about the end of the week and soon disappear *The regional lymph nodes usually* are swollen *and tender* as one would expect since the vaccine bodies continue to multiply in the nodes

Revaccination — Since the immunity from vaccination diminishes gradually with age it is necessary to revaccinate at school age and again whenever there is any possible exposure to smallpox Students going to college army and navy recruits and travelers to backward regions should be revaccinated because contacts with the public are greatly increased and because an attack of smallpox no matter how mild would cause much loss of time to the patient and great inconvenience to the community The reactions following revaccination are modified by the fact of primary vaccination and in general are grouped in three classes the immediate or immune reaction the vaccinoid or accelerated reaction and the full development of the process which is called vaccinia

The nature of the reaction is determined by the amount of immunity

remaining from the primary vaccination or a previous revaccination If the amount of immunity remaining is great we get the immune reaction This consists merely in the appearance of a papule which develops in 24 to 48 hours and does not go on to the formation of a vesicle or pustule The accelerated reaction is intermediate between the immune reaction and vaccinia The time and extent of each stage is shortened and diminished and the whole process is over in a week or ten days, depending upon how much immunity remains from previous vaccination The full reaction, or vaccinia, such as we have in primary vaccination is very rare on revaccination but it may occur just as second attacks of smallpox itself sometimes happen and is good evidence that that particular individual has lost all of his immunity Vaccination may produce a positive result even when the patient at some time in the past has recovered from smallpox and presumably for the same reason In vaccination or revaccination one obtains either vaccinia, an accelerated reaction or an immune reaction If none of these three occur it is because the vaccine itself was dead, or because the technique was in some way faulty

New Methods —Although the vaccine now obtainable everywhere is excellent and quite satisfactory yet many studies are being carried out with the purpose of finding some method of preparing the vaccine which will be still better Rivers and his collaborators (1935) have described the preparation of Jennerian vaccine on Maitland s medium hashed chicken embryo suspended in Tyrodes solution and its use in children by the intradermal method When the vaccine is given by hypodermic syringe into the skin, and the point of entrance of the needle is wiped with alcohol or acetone the process may run its entire course without any breakdown of the superficial layers of the epidermis and no scar results While the results have been very encouraging the method has not yet been adopted by the official health agencies Fair numbers of the children vaccinated when retested after several weeks or months were found to be susceptible to ordinary dermal vaccine The reason is not yet clear but it may be that the number of living active elementary bodies in the suspension is too small

Another new vaccine has been prepared and used by Goodpasture (1935), which is made by growing the seed vaccine on embryonated eggs After the egg has been incubated for fourteen days it is ready for the inoculation of the vaccine virus The virus is rubbed over the chorio allantoic membrane and for the first few generations three or four the virus is harvested after seventy two hours but later generations can be harvested after forty eight hours The membranes are frozen and, while in the frozen state are ground up in a cold sterile mortar and then four

parts of 50 per cent glycerine are added The virus is sterile when harvested and does not need long storage to free it of contaminating bacteria It is titrated on the rabbit in the usual way to determine the ultimate dilution to be used in practice The results obtained in human vaccination have been fully as good as those following vaccination with calf lymph Goodpasture s vaccine has not been used intradermally but by the scratch or multiple pressure method and the results are quite promising

A third method has been recommended by Henderson and McClean (1939) who use filtered calf lymph intradermally The authors found that immunity to dermal vaccination did not follow unless a vesicle formed at the site of the intradermal inoculation When a vesicle did form the immunity to dermal vaccination was satisfactory

While all these methods of preparing vaccine are interesting and promising they are however still to be regarded as in the experimental stage

Complications of Vaccination

In the past there was much discussion of the possibility of transmitting disease by vaccination and in the days when arm to arm vaccination was practiced it was a problem Today however the problem no longer exists as only glycerinated calf lymph is used Calves do not have syphilis and tuberculosis and other diseases of cattle transmissible to man are excluded by the regular autopsy carried out on the calf before the vaccine is released for use

Tetanus has occurred in the past but its origin has been traced much more often to secondary infection through contaminated dressings and to shields and to ivory or bone points than to the vaccine itself Shields should not be used and bone points are no longer furnished in the United States by our vaccine establishments Tetanus is a disease which is endemic in certain regions as in the truck garden region of Long Island N Y and in Puerto Rico for example and in these regions special care must be exercised in all operations and in the care of all injuries including vaccination If the special danger in such limited regions is recognized the remedy is simple

Encephalomyelitis of Vaccinia

Encephalomyelitis is a rare but serious complication The disease appears from ten to thirteen days after vaccination most cases developing on the twelfth day the illness begins suddenly with headache vomiting and deviation of the eyes dullness and drowsiness which rapidly increases

to coma In some cases spastic paralysis may occur, or meningeal symptoms may predominate with rigidity of the neck a positive Kernig s sign, eye changes and convulsions Death may occur in two to four days The vaccination itself is almost always quite normal in appearance and behavior Many variations in the symptoms have been described and the differential diagnosis is not always easy It is well to make a blood culture in all cases and to secure autopsies on fatal cases to exclude other general infections The cell count of the cerebrospinal fluid may show one hundred to one hundred and fifty mononuclear leucocytes for each cubic millimeter The leucocyte count of the blood may increase to ten to twenty thousand

The mortality varies in different regions, among the cases studied in the report of 1928 it was 58 per cent among the 71 cases studied by Armstrong (1932) it was 37 per cent Recovery usually is complete, al though occasional cases of epilepsy and mental changes have been re ported but in these cases there is some question as to the real diagnosis

The treatment is purely symptomatic lumbar puncture will lower the pressure of the cerebrospinal fluid and may be helpful the convulsions may be controlled by sedatives and good nursing Not much can be ex pected from the administration of the serum from convalescents from vaccination as the therapeutic use of immune sera after the development of virus diseases such as poliomyelitis has not been successful

Post vaccinal encephalitis has been recognized since about 1922, when many cases were reported from England and Holland A few cases con tinue to occur in the United States and other countries One of the best of the early studies was that of Turnbull and McIntosh (1926) They studied 7 fatal cases very thoroughly and found that the disease more properly should be called encephalomyelitis following vaccination Some autopsies showed also a leptomeningitis Death occurred on the four teenth fifteenth seventeenth (three cases) and eighteenth days after vaccination

The histology of the lesions is quite different from that found in poliomyelitis and epidemic encephalitis The cardinal differential fea ture by which the conditions can be separated at a glance is the occur rence in the post vaccinal encephalomyelitis of perivascular zones of softening of white substance They conclude that vaccination was a definite causal factor

Many studies have been made since 1926 and we are still ignorant of the true nature of this complication The fact that Turnbull and McIntosh isolated vaccine virus from the central nervous system of three of the cases they studied has not the significance which they attributed

to it We know that in animals the virus is distributed throughout the body including the brain but that ordinarily it does not produce lesions and that the virus rapidly disappears In many cases of encephalitis it has been impossible to isolate any virus

The immunity of the vaccinated person gradually builds up and there is some immunity by the end of the first week and by the end of the second week there is so much immunity that the vaccination lesion rapidly subsides It is noted that most cases of encephalomyelitis sicken during the second week most often on the eleventh day following vaccination that is at the time when the immunity is already well developed (Finley 1938) This makes the whole situation difficult to understand An encephalomyelitis of similar character is found also in the course of variola itself and in a number of other infectious diseases measles mumps influenza antirabies treatment and perhaps varicella The relations of all of these are not fully understood

Many attempts have been made to show some contamination of the vaccine virus with some other virus but without success the cases of encephalitis have not been caused by any one strain of vaccine virus and it seems quite evident that the cause of the nervous involvement does not lie in the vaccine virus but in the host that is the patient Putnam (1935 35-6 and 37) has proposed an interesting hypothesis that the areas of softening and demyelization are caused not by any virus but are the results of venous thrombi of the smallest veins He *thinks that the cause of the brain and cord changes are secondary to an abnormal clotting mechanism of the blood occurring only in certain persons* This interesting suggestion would account for the anatomical and mechanical features of the disease which follows infection with so many different viruses and even of chemical agents such as carbon monoxide

Kaiser and Zappert (1938) and many others have pointed out the lack of correlation between the number of cases of encephalomyelitis and the number of vaccinations carried out in any area Kaiser notes that most vaccinations in Austria are done in Vienna but that most cases of post vaccinal encephalitis occur in the provinces sometimes in small groups of cases in the villages the vaccine used being the same in both regions

The importance of primary vaccination at school age or later in causing this complication is shown wherever it has been studied The encephalitis rarely follows revaccination In 71 cases occuring in the United States reported by Armstrong (1932) only 2 followed revaccination It has occurred most frequently when primary vaccination was

carried out at school age and it is almost unknown when only infants are vaccinated As a result of studies carried out in many places certain conclusions have been drawn and recommendations made for routine vaccination Since the complication is very rare in infancy the Rolleston Committee Report (1928) advises that infants be vaccinated some time between two and six months of age and that revaccination be carried out at school age, five to seven years and again at fourteen to sixteen years Kaiser (1938) found that the encephalitis occurred in the spring and early summer in most cases and he suggests that vaccination be carried out preferably in the colder months of the year In addition the Committee recommended that only one insertion be made and that of the smallest possible size

Fortunately the number of vaccinated persons manifesting this complication seems to be diminishing

Post vaccinal encephalitis is discussed also by A H Gordon in Chapter III A Volume VI of Oxford Medicine

Contraindications to Vaccination

In the presence of an epidemic of smallpox there are practically no contraindications except the presence of some serious enfeebling disease The other acute infectious diseases measles mumps etc are not contraindications Young children with extensive eczema should not be vaccinated as the vaccinia may spread rapidly over the whole eczematous area and even be fatal

Conclusion

In conclusion it seems desirable for us to remind ourselves of a somewhat paradoxical situation which presents itself with reference to this disease and its prevention When smallpox is prevalent the medical and public health professions and the public demand vaccination of the whole susceptible population When smallpox is not prevalent and particularly when there have been no outbreaks in many years the public forgets the danger and vaccination is neglected but it is exactly under such circumstances that the medical profession and the public health service should be most active in seeing that all infants are vaccinated and all school children are revaccinated

There is no other way of preventing the disease and if a susceptible population is permitted to grow up an epidemic sooner or later is inevitable

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CHAPTER XXIV

CHICKENPOX

By GEORGE DOCK

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Synonyms—Varicella (Latin) varicelle (French) Windpocken Wasserpocken (German) varicella morviglione (Italian)

Definition—Chickenpox is an acute infectious disease of unknown etiology characterized by an eruption in which a macule passes rapidly to a vesicle with fever and mild general symptoms

ETIOLOGY

On account of its resemblance to mild smallpox an identity has been supposed but many empirical facts oppose the theory The most important facts are varicella has never been known to originate smallpox and vice versa inoculation of chickenpox has often been practiced and in most cases with negative results when it succeeds (Steiner 1875) it produces varicella and never smallpox even in unvaccinated subjects neither disease protects against the other

Chickenpox is easily communicated being rivalled in that respect only by measles but the mode of propagation is not known The disease is endemic in large cities and shows small epidemics at times in which it seems that the infection easily spreads through the air and by touch or through fomites It is also inoculable but with some difficulty Three fourths of young children exposed and half of those over two years of age often become infected in epidemics There is no seasonal relation In cities

found especially in cases that prove to be severe but the eruption appears so early that prodromal fever cannot be spoken of

The initial rashes have been seen especially an ephemeral erythema suggesting scarlet fever over a large part of the body but sometimes roseolar or rubeolar Coincident scarlet fever or measles must be considered in such cases Comby[8] thinks these rashes are due to benign streptococcus infection

The specific eruption begins as red macules little or not at all elevated but in some cases with a palpable thickening The vesicle forms rapidly is round or oval in outline conical or with a rounded top or rarely with a small depression By the second or third day the larger lesions very much resemble what the genuine smallpox are in the fifth day" (Heberden) They vary from 2 to 15 mm in diameter usually 3 to 5 The top is thin and white the contents clear pale yellow later turbid The fluid usually not always flows freely if the vesicle is punctured There is often a narrow bright red areola especially around the lesions on the back

The lesions begin on the scalp face and body about the same time Later the arms and legs are involved The distribution is usually more dense on the trunk Hands and feet including palms and soles are not spared Irritation of the skin by rubbing prolonged decubitus counter irritants flea bites and dermatitis often cause a local increase of the eruption P Gautier[9] has seen similar effect in sunburn during heliotherapy The total number ranges from a few to several hundred and may even be confluent In contrast to smallpox new lesions spring up among the earlier ones so that a variety of stages can often be seen as long as the eruption lasts and with a more orderly progression of lesions

Some of the macules or papules undergo resolution Vesicles usually remain for several hours to a day then become more turbid lose their tense appearance and become wrinkled Some are ruptured by rubbing and scratching By another day that is the third fourth or fifth but sometimes much later the vesicles are dried up forming thin brown crusts When they drop off from the fifth to the twenty first day shallow scars are left or in rare cases with the process involving the papillary layer deep ones but without the fine pits so characteristic of smallpox

The visible mucous membranes are affected at the same time as the skin The buccal surface hard palate and lips are chiefly involved but also the tongue gums tonsils larynx conjunctiva vagina and prepuce These lesions break down rapidly as in smallpox leaving shallow ulcers with red edges

The temperature rises rapidly has no definite type remains up for from one to seven days and is usually highest while the eruption is forming The pulse is usually only slightly accelerated more so in severe cases

chickenpox occurs every year in schools contagious disease hospitals and asylums and is so peculiarly a children s disease that many experts deny its occurrence in adults which was recognized by Heberden Those who see young adults coming from the country into cities or as recruits in armies can often observe the disease in them and it may occur in old age It often appears in epidemics with scarlet fever and whooping cough

Herpes Zoster and Chickenpox—In a considerable number of cases herpes zoster and chickenpox have shown curious relations Patients with zoster have had chickenpox within two weeks and cases with chicken pox have occurred in families one member of which had zoster at the time or a short time before Sometimes herpes zoster and chickenpox occur in two members of a family at the same time[1 2]

Pathology and Histology

Tyzzer[3 4] Unna and others have examined the affected skin and find minute changes in the early macule The nuclei of the epithelial cells in the middle layer undergo direct division forming giant cells with the nuclei massed together The cytoplasm swells and the cells often reach very large size Both nuclei and plasma liquefy serum exudes between some cells forming multilocular lesions at first but the septa soon break down and form a single cavity with slight necrosis of the walls There is no umbilication as in smallpox and vaccination except in rare instances in which sweat ducts probably produce it The contents of the vesicles contain giant cells and a few leukocytes No characteristic parasites have been demonstrated but Tyzzer Paschen[5] Gins[6] and others describe cell inclusions unlike those of vaccinia and very rare in smallpox Some of these are as large as red blood corpuscles and stain faintly with eosin Further observations are needed In the majority of cases recovery occurs so that the condition of the internal organs is not known

J A Kolmer[7] proved the presence of antibodies in contents of the vesicles and crusts The antigens are different from those of smallpox

Symptoms

Chickenpox has a stage of incubation of ten to twenty one days In this time there are no symptoms and the first sign of disease is usually the vesicular eruption When the disease breaks out in an institution and cases can be observed from the beginning malaise pallor loss of appetite restlessness disturbed sleep and slight elevation of temperature can be

time the clinical diagnosis may often be made In all doubtful cases the patient should be isolated from smallpox as well as from the public

Impetigo contagiosa is likely to be confused in later stages of the vesicle when the lesions have been injured by scratching Herpetic lesions even in herpes zoster have often been confused also dermatitis herpetiformis and pemphigus Careful attention to the history complete examination of vesicle contents and corneal inoculation should prevent error

Prognosis

Chickenpox in a previously healthy person put under proper care early always recovers In those recovering from other diseases or cachectic from any cause secondary infection gangrene and death sometimes occur The condition of the kidneys must be investigated as early as possible and the findings used in prognosis

Treatment

Isolation should always be practiced in case of doubt In unmistakable chickenpox the fashion of allowing it to spread among young persons has little danger but its disrupting effect on schools shows the unwisdom of so helpless a practice

The patient should be in a well aired room in bed when the temperature is elevated lightly clad The body and surroundings should be kept clean Light diet and sufficient water should be used with fruit juices or fruit

If there is much irritation boric ointment mentholated oil (½ to 1 per cent) or carbolized ointments or solutions may be used Purulent lesions *should be opened or touched with pure carbolic acid or alcohol*

Smallpeice Kling May Michael[10] and others inoculated vesicle contents in order to immunize with only partial results A F Hess[11] gave intravenous injections of vesicle contents in salt solution and secured almost absolute immunity Sterilization of the material would seem safer though the amount of lymph used would probably have to be increased in further tests of this method Syphilis in the donor should be excluded

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Complications

Albuminuria is a frequent accompaniment of chickenpox but rarely leaves sequels like those of scarlet fever and measles Hemorrhagic chicken pox is a rare and sometimes fatal form and is seen especially in delicate children Gangrene is the most serious complication It probably occurs in most cases from scratching with dirty finger nails Other septic skin diseases occur but are rare

Parotitis thyroiditis otitis media laryngitis bronchitis and bronchopneumonia have all been observed and should prevent the habit of looking on chickenpox as a trivial ailment not requiring a physician Synoviti occurs and may even become purulent Periostitis meningitis encephalitis and various partial paralyses have been observed after chickenpox

Diagnosis

The differential diagnosis is the most important matter in connection with chickenpox In some cases the diagnosis may be impossible in many others though possible a wrong conclusion is made and a patient with chickenpox may be sent to a smallpox ward or an epidemic of smallpox originate in a case thought to be chickenpox Exposure to one or the other disease and vaccination history and condition must first be considered If initial symptoms and fever have been recognized before the beginning of the rash smallpox is more probable If there is no such history but a temperature of 101°F 102°F or more with vesicles well developed chicken pox is probable A history of prodromal rash is not as useful as one that can be seen by the physician and even then in a mild case of smallpox may not be possible to distinguish from that of chickenpox The location of the eruption with the almost constant preponderance on the back and trunk in chickenpox is very important also the rapid formation of the vesicles and the greater irregularity of the stage Lesions on the mucous membranes the palms and soles do not exclude chickenpox The result of puncturing to show the unilocular character of the chickenpox vesicle is often misleading Examinations of stained films showing giant cells and no Guarnieri or elementary bodies should only be depended upon when the results are clear Intracellular bodies in varicella are not so sharp round and glistening as in smallpox Inoculation of a rabbit s cornea may assist but requires at least 24 to 48 hours and if the macroscopic result is doubtful the microscope will have to be used on sections of the lesions in order to prove the absence of Guarnieri bodies In that

CHAPTER XXV

ONYALAI

By MAJOR JAMES STEVENS SIMMONS Medical Corps U S Army

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Definition — Onyalai is an acute disease of unknown cause characterized by sudden onset with symptoms suggesting an intoxication, accompanied by hemorrhages into the internal organs and the development of bullae containing uncoagulated blood in the skin and mucous membranes These hemorrhagic bullae are especially noticeable on the tongue soft palate and buccal mucous membranes The disease is not uncommon in certain parts of Africa where the natives consider it to be very fatal

HISTORY AND DISTRIBUTION

In 1904 Wellman published a note in which he described the disease designated as hemorrhagic bulla (native name onyalai) and stated that it was a common and very treacherous disease greatly feared by the natives of Angola who believed that it usually resulted in death Later during the same year Massey also in Angola published records of three cases of onyalai selected from a number seen by him during five years and stated he had heard that the disease also existed in the far interior of Africa In 1905 Feldman reported a disease called edjuo among the natives of Bukoba in East Africa which Mense considered similar to onyalai Mense while on the Congo observed a disease known by the Unyamwesi people as kafindo which spread across equatorial Africa and which resembled onyalai rather closely Wellman in 1908 stated that he believed edjuo and kafindo to be identical with or closely related to onyalai

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11 HESS, A F and UNGER L J Am Jour Dis Child Chicago 1918 XVI 34

Wellman also described three cases all of whom had symptoms of disturbance of the central nervous system One of these was a young woman in ruddy health She was laughing and playing in the evening of her attack Suddenly she complained of being tired and in an hour or so bullae appeared in her mouth She steadily grew more depressed and died about eight o clock the next morning with all the symptoms of cerebral hemorrhage Another fatal case in the same house a strong young man being the victim presented exactly the same symptoms A third fatal case showed no vesicles either in the mouth or in the skin Apparently recovery from an attack of onyalai fails to immunize the individual as the disease may recur several times

Prognosis

Both Wellman and Massey noted the fact that the natives consider onyalai to be extremely dangerous because of its high case fatality Wellman remarked that he was once inclined to treat the native view very lightly but after seeing cases die a few hours after the beginning of an attack he had reversed his opinion He adds that judging from native reports the malignancy of the disease varies in different seasons and localities He reported observations on fourteen patients three of whom died Massey published three case histories and remarked that all of his patients had recovered but that he had seen one fatal case With the limited information available it is imposs ble to estimate either the case fatality or the mortality of this disease

Treatment and Prevention

Wellman who tried quinine alkaline salts oil of turpentine acetate of lead tannic acid ergot and suprarenal extract with no perceptible results thought some of his cases were benefited by large doses of arsenic He reported that the natives used various plants including Ceigera Wellmani Hutch and Albizzia anthelmintica, A Brogn Large doses of bicarbonate of soda and cod liver oil were used by Massey It is apparent that these various substances have been used empirically and that no specific agent has been found for the treatment of onyalai There is no available information concerning the prevention of the disease

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Etiology

The cause of onyalai is not known The studies of Wellman led him to conclude that the disease is not a manifestation of malaria, and that it is not due to accidental or purposeful poisoning either with arrow poisons or the medicinal plants used by the natives Mense in discussing kafindo suggested that it might be caused by poisoning with Euphorbiaceae or other native plants Wellman observed that certain cases of onyalai resembled the poisoning produced by the bite of the puff adder, Bitis arietans, but believed that the disease was not due to this cause He was unable to incriminate either bacteria or protozoa as the causative agent

Symptoms

The onset of onyalai is abrupt While apparently in perfect health, the patient suddenly feels weak and within a few hours may appear dazed and show signs of extreme lassitude The eyelids appear heavy, there may be slight congestion of the conjunctivae and in certain cases the parotid glands are tender Two-thirds of the cases have slight fever, but rapidly fatal cases have been observed in which there was no elevation of the temperature Some of the patients complain of numbness and pain in different parts of the body The appetite is poor and the tongue swollen and painful The characteristic bullae may appear in the mouth pharynx, oesophagus stomach and intestines, and also on the skin over various parts of the body They range from the size of a split pea to large irregular, umbilicated blisters several inches in diameter In certain cases the bullae are scarce and may be so small as to be overlooked They extend deeply into the submucosa or the corium and are crossed by fibrous trabeculae the interstices of which are filled with partially coagulated blood giving a dark appearance under the skin or mucous membrane The erythrocytes are partially disintegrated

One of the first signs of the disease may be the appearance of blood in the mouth or the vomiting of blood which in some cases is accompanied by a bloody diarrhea Hematuria has been observed and hemorrhages may occur in the brain, pancreas liver or spleen Wellman described the disease in a 14 year old native house servant as follows The boy, a full blooded Kaffir, was apparently in perfect health Without complaining of any subjective symptoms whatever he noticed one morning blood in his mouth No well defined vesicles could be seen The blood seemed to come from around the teeth He went that afternoon to his kraal The next day he vomited dark, altered blood in large quantities passing the same in his urine and feces He died the third day from the onset of the disease He gave a history of one previous attack of the trouble "

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RABIES

By HARALD N JOHNSON

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from 10 days to one year The disease is characterized by great excitability spasmodic reflex contractions of the muscles of respiration and deglutition convulsive seizures and progressive sensory and motor paralysis The disease invariably is fatal in man

The histopathological changes produced by the virus are practically confined to the nervous system and salivary glands The affected cells are destroyed with little or no secondary inflammatory cell infiltration The occurrence of specific intracytoplasmic inclusion bodies in certain nerve cells of the brain is diagnostic but these are not always present especially where the disease was of short duration

Epidemiology

Distribution

Rabies is a disease which has been known since ancient times The aggressive and vicious character of animals afflicted with furious rabies caused the people of ancient Rome Greece and Egypt to believe that such animals were inhabited by demons Stone murals from this age depict mad dogs and Greek mythology has references to the disease and mentions certain gods as having the ability both to make animals mad and to heal them

Democritus in the fifth century B C probably was the first physician to write about the disease He described it as an inflammation of the nerves resembling tetanus in so far as it was accompanied by spasmodic contractions of certain muscles Aristotle 322 B C gave an account of the disease in dogs and other domestic animals Celsus 100 A D gave a detailed account of the disease in man and practised cautery of wounds resulting from the bite of rabid animals It is apparent from these accounts that the disease as we know it today is much the same as it was in ancient times

Europe – Rabies is reported to have been prevalent in France in 1271 and in Spain during 1500 Abelinus in 1634 described an epizootic of canine rabies in the German provinces of Rhineland and Saxony

The disease spread over most of Europe during the early part of the 18th century, beginning in Italy in 1708 invading Germany and France in 1719 and England in 1734 The majority of human rabies cases during this period were from exposure to rabid wolves and the survival and spread of the disease seemed largely dependent on this animal

There was subsequently a period of low incidence until 1800 when rabies became epizootic in Germany In Prussia alone there were from

DEFINITION

Rabies is an acute specific infection of the central nervous system caused by a filterable virus transmitted to man by infected domestic or wild animals usually the dog by means of a bite or scratch and the contamination of resulting wounds or abrasions with infected saliva

The average incubation period is 42 days with a possible range of

rabies gradually became more prevalent until 1895 during which year there were 20 human and 672 dog rabies cases reported in England and Wales The dog control measures again were intensified and enforced throughout Great Britain and in 1897 made even more rigid so that from 1899 to 1902 there were only isolated cases of dog rabies with no human cases reported and by 1903 the disease was completely eradicated Although rabies was again introduced in 1918 by a dog carried over from the continent by plane by 1921 England was free of rabies and has re mained so to the present time

Rabies in England was propagated almost entirely by dogs The only wild animals affected appeared to be deer and two interesting epi zootics occurred in that species In 1886–1887 rabies became epizootic in the protected herd of deer in Richmond Park and in 1887 a total of 257 of these animals died of the disease A similar epizootic occurred in the deer herd at Suffolk in 1888 The latter outbreak was traced to a rabid dog which had bitten one or more of the deer and 500 of the 650 animals in this herd died of rabies

Africa and Asia — Rabies has been prevalent in parts of these con tinents since ancient times and seems to have been constantly present in Egypt and Arabia Although rabies has been reported in Algeria Tunisia Anglo Egyptian Sudan and India there are no satisfactory records of its progressive geographical distribution The disease has been especially common in India The first authentic case of rabies in South Africa occurred in 1893

It is probable that rabies has been present in China since ancient times It was present in Indo China and the Dutch East Indies before 1900 Rabies first appeared in the Philippine Islands in 1900 and in Japan in 1901 Australia and the Hawaiian Islands have remained free of the disease

North America — The earliest account of rabies in North America was in 1768 when the disease first appeared in the vicinity of Boston During 1770–1771 it increased in prevalence in this area and spread to the fox species The disease soon appeared in Pennsylvania Mary land and North Carolina and was especially prevalent in and about Philadelphia By 1785 the disease was enzootic throughout New England and had appeared in the plantation areas of the South By 1860 it had invaded most of the states east of the Mississippi and had been reported as far west as New Mexico By 1899 the disease had invaded California and since then has remained enzootic over most of the United States

Several major outbreaks of rabies in wild animals have been reported in North America In 1875 the disease appeared in the small spotted

200 to 260 human rabies deaths annually between 1800 and 1810 The incidence then increased until 1819, when 356 human rabies fatalities were reported Rigid dog control measures then were introduced and canine rabies became relatively rare The disease was however, continued in the fox species and from 1803 to 1828 there were repeated epizootics of fox rabies in Southern Germany and in Switzerland

In 1815 rabies appeared for the first time in Denmark and Norway In 1824 the disease was introduced into Sweden Rabies was quickly eliminated from these three countries by sanitary measures and they have remained free of the disease to the present time Rabies was reported in Russia during 1810 and subsequently became highly prevalent among the wolves which were abundant in that country

Beginning in 1852 there were repeated epizootics of canine rabies in Austria Germany and France From 1852 to 1853 the disease was highly prevalent in Prussia and Hamburg and from 1861 to 1865 in France the Rhineland Wurtemberg Saxony and Austria The disease reached a maximum incidence in Bavaria and Prussia during 1871

From 1875 to 1914 the general incidence of rabies was low over most of Europe Epizootic canine rabies occurred in Hungary from 1888 to 1893 in Austria from 1891 to 1900 in Germany in 1898 and again in 1903–1904 and in France in 1899–1900 It was noted that the epizootic in Hungary began along the Russian and Rumanian frontiers where wolves were abundant and were known to be infected with rabies

Prior to the World War I rabies was quite prevalent in Poland Rumania Serbia Bulgaria and Russia During this war there was a general increase in incidence in all the warring countries The disease became especially common in France near Paris in 1919 in Germany in 1923–1924 and in Poland and Russia in 1924–1925 In more recent years the incidence of rabies has been relatively low in Western Europe but has remained high in Poland and the Balkan countries

Great Britain — Rabies was first reported in England in 1734 During 1757 large numbers of horned cattle died of rabies in England The disease was first reported in Ireland in 1807 From 1853 to 1885 there was a gradual increase in the incidence of rabies both in man and animal During 1885 27 human rabies deaths were reported in London but in 1886 dog control regulations were enforced rigorously in that city and no human cases developed The emergency sanitary measures then were relaxed and canine rabies increased until 1889 when there were 10 human cases in London out of a total of 30 for all of England and Wales The dog control regulations then were generally enforced with a sharp drop in the incidence of the disease The regulations again were relaxed and

West Indies and South America — Rabies was introduced into the West Indies in 1873 South America appears to have been free of the disease until the latter part of the nineteenth century In recent years canine rabies has been uncommon in the northern part of the continent but a new vector the vampire bat has become a dangerous source of the disease in Brazil and Venezuela

Influence of Climate and Season

Rabies has been reported from the arctic to the highly tropical regions Climate seems to have no effect on the character or incidence of the disease There is an old superstition that rabies is most apt to occur in the fall It has however been found from repeated analysis that the peak of incidence falls in the late winter and spring period This may well be due to the fact that the stray dog wolf and fox are the principal vectors and during these months will travel about in search of food and mate Epizootics of rabies may and do occur at any time of the year

Relation to Human Population

Rabies is rare in sparsely settled areas unless it becomes established in an abundant species of wild animal In thickly settled areas the disease once established occurs in proportion to the number of stray dogs Periods of rapid geographical distribution of the disease usually are associated with wars or migrations of civilians

Influence of Race Sex and Age

There is no satisfactory evidence to indicate differences in susceptibility of the white yellow or black races Males and females appear equally susceptible although incidence is higher in males The majority of cases of human rabies occur in children but this cannot be considered as proof of a greater susceptibility on their part They are more liable to exposure due to their fondness for playing with animals and lack of defense if attacked

Cyclical Character

Major epizootics of rabies develop from time to time but the cycle is not regular Epizootics are short lived in any one place rarely lasting more than one year After the epizootic subsides sporadic cases continue

skunk species in Kansas and from 1907 to 1910 skunk rabies was prevalent in Arizona. Epizootic fox rabies occurred in Massachusetts in 1812, in Alabama in 1890, in Alaska in 1915 and in Georgia in 1940–1941. The extensive epizootic of rabies in coyotes of Nevada, Oregon and California during 1915–1916 is a good example of the rapid spread of the disease in an abundant species of wild animals.

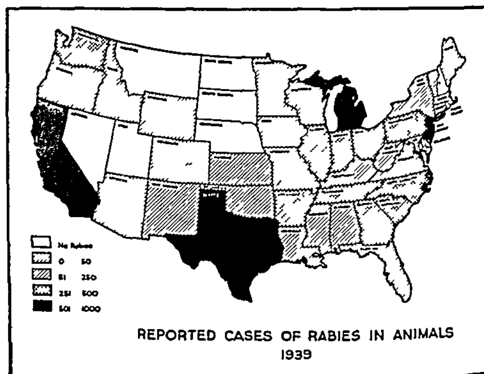


FIG. 1. Chart showing the relative incidence of rabies in animals during 1939 based on the reports of the Committee on Rabies of the U. S. Livestock Sanitary Association.

From 1923 to 1938 the number of human rabies cases reported annually in the United States varied from 53 to 103. During this period 44 of the 48 states reported one or more cases of human rabies.

Rabies was reported in Greenland in 1859. Expeditions visiting the island in 1866–1867 and in 1875–1876 noted that the Eskimo dogs occasionally developed the disease. Rabies was prevalent among the arctic wolves of the Barren Lands in 1897. Rabies has occurred in most parts of Canada, but in recent years, due to vigorously enforced quarantine restrictions, the disease has decreased in incidence almost to extinction. Rabies was epizootic in the coyotes of Northern Mexico in 1892. The disease has remained enzootic in Mexico since that time.

Human Mortality and Attack Rate

The mortality statistics are diverse Bouley under the auspices of the French Committee of Hygiene collected 383 cases of exposure to rabid dogs from records covering 1862 to 1872 with 180 deaths (47 per cent) Renault reported that of 254 persons bitten by rabid wolves 164 (65 per cent) died of rabies These are in sharp contrast to other mortality statistics Faber reported that only 36 (6 per cent) of 597 persons bitten by rabid animals developed rabies Kirchner of Prussia recorded 38 deaths (3 per cent) among 1 453 persons bitten by rabid dogs Schuder noted only 1 325 deaths in a group of 14 959 persons bitten by rabid animals (9 per cent) Von Frisch called attention to the factor of septic infection as a cause of death among persons bitten by rabid animals especially wolves Tetanus may occur as the result of puncture wounds produced by rabid animals

It is interesting to note that Youatt of England published a report of 400 persons bitten by supposedly rabid dogs and given only local treatment with no deaths from rabies Ekstrom in 1830 reported that of 106 persons bitten by rabid animals during the rabies epizootic in and about Stockholm during 1824 and treated by incision and cautery of the wounds none succumbed to rabies There were only 5 cases of human rabies during the entire epizootic One of 11 people bitten by one rabid dog did not allow local treatment and developed rabies

There are no satisfactory data available concerning the attack rate for rabies in man following exposure by the bite of a rabid dog It has been the practice to give the antirabic vaccine treatment to all persons exposed since the preventive treatment was first introduced in 1885

The location of the bite is an important factor in the susceptibility to rabies Dobert noted 12 cases of rabies among 118 persons bitten on the head (10 per cent) compared with 24 cases among 1 ,51 persons bitten on the arms (2 per cent) one out of 564 bitten on the legs (0 2 per cent) and no deaths among 72 bitten on the trunk

Another factor which reduces the attack rate is the occasional absence of the virus in the saliva of vicious rabid animals The death rate may be lower in modern times due to more adequate cleansing of wounds It is probable that the bite of rabid wild animals is more infectious than that of rabid domesticated dogs

Review of Investigative Work

The causative agent of rabies was shown to be present in the saliva of rabid dogs by Zinke (1804) and this was confirmed by Gruner and

to occur from year to year unless rigid control measures are adopted and enforced It appears that the virus, at times naturally tends to assume the characteristics of fixed ' virus i e, increased neurotropism and a corresponding decrease in the ability to invade the salivary glands Natural propagation in one species of animal may increase or decrease the pathogenicity of the virus for other species

Natural Vectors

The early history of rabies shows that the wolf and related wild canine species have played a major rôle in the perpetuation of the dis ease In more recent times the dog, especially the stray and semi wild variety has been responsible for the continuation of the disease in the thickly inhabited sections of the world The feline species apparently are only secondary vectors except for the related meercat and mongoose species in South Africa and India The vampire bat acts as a true carrier and is able to perpetuate the disease It is possible that a symptomless carrier state may develop occasionally in the canine species There is no evidence to suggest that insects or rodents play any part in the propaga tion of the disease

Source of Human Infection

Infection from the dog or domestic cat accounts for all but one to two per cent of human infections Infection from rabid wild animals rarely occurs in the United States In South America the vampire bat may infect man In South Africa and India human infections have been re ported from the bite of the meercat mongoose jackal and monkey Human infections have been reported in rare instances following exposure to rabid domestic animals such as the cow There is apparently little danger in handling objects contaminated with the virus such as carcasses hides rope and bedding Infection from drinking the milk of rabid cows or eating the meat of animals infected with the disease is extremely un likely While exceedingly rare infection from man to man is pos ible either by bite or by exposure of fresh skin abrasions to saliva from such cases As maniacal and murderous activity is uncommon in human rabies and heavy sedation is given routinely there is little danger of infection from man Laboratory infections are uncommon and have occurred only when the person was bitten by an experimentally infected animal or by accidental injury when performing autopsies

by other investigators the preventive treatment was tried in a human exposed to rabies In July 1885 Joseph Meister a peasant boy who had been severely bitten by a rabid dog was brought to Pasteur and in view of the serious nature of the exposure and due to the plea that something be done the treatment used for the experimental studies on dogs was given to the boy The treatment appeared to be without ill effects and the boy remained well This was hailed as a remarkable feat and soon other exposed individuals came to Pasteur for the treatment Though the majority of the treated persons did not contract rabies an occasional case did come down with the disease despite the treatment and therefore a more intensive scheme was devised beginning with more than one injection daily for the first 5 days and continuing the injections for 15 to 21 days depending on the severity of the exposure Because so few of the exposed individuals developed rabies following the improved treatment, no further experimentation was carried out with dogs and it was felt that the worth of the procedure had been proved

Besides developing a method of vaccination Pasteur made numerous other contributions regarding the nature of rabies virus He noted that guinea pigs fowl monkeys sheep and other warm blooded animals were susceptible that dumb and furious rabies was the same disease and that the virus was present in the nerves and salivary glands

The studies of Pasteur stimulated widespread interest in rabies re search Subsequent reports on prophylactic and post exposure vaccine treatment experiments in animals were conflicting

As the Pasteur vaccine treatment occasionally failed to prevent the development of rabies in exposed persons modifications of the dried cord method and new methods of vaccine production were introduced The only significant modifications of the dried cord method were the intro duction of glycerin preservation by Calmette for storing the dried cord used in treatment and intensification of the treatment by beginning with cord material dried only 5 to 8 days The subcutaneous injection of live fixed virus appeared to be without ill effects in man so the tendency was to increase the dosage of virus Ferran of Barcelona in 1888 introduced the use of fresh fixed virus His plan of treatment was based on the assumption that drying only killed some of the virus and the amount of active virus could be reduced similarly by dilution He used a 1 to 100 suspension of fresh rabbit fixed virus cord material and gave 3 in jections daily for 5 days Borregi began using this method in his clinic in 1889 Over a short period of time 5 patients died of vaccine rabies and the clinic was closed by order of the Italian government This temporarily discouraged the use of fresh fixed virus Hogyes in 1897

Salm (1813) Magendie and Bouchet (1813) were able to infect dogs with saliva obtained from a human case of rabies and so proved that hydrophobia in man and rabies in the dog were synonymous. In 1, 1 Van Swieten described the occurrence of paralytic rabies in man. Galtier of Lyons (1879) demonstrated that rabbits were susceptible to rabies.

The modern concept of rabies and virus diseases in general was developed by Pasteur. He first became interested in the disease in 1880 when he saw a young girl dying of rabies at the Saint Eugene Hospital in Paris. He immediately began an intensive study of the disease in collaboration with Chamberland and Roux. The discovery that the virus was always present in the brain of man or animals dying of rabies and the development of a trephine technique whereby rabbits could be consistently infected with suspensions of infected brain material formed the basis for the epoch making studies of Pasteur. He was soon able to show that the causative agent was invisible in microscopical preparations and would not grow in culture media in the manner of bacteria. He therefore called the infective agent "virus" from the Latin word meaning poison. Serial intracerebral passage of the virus in rabbits gradually decreased the incubation period but finally this reached a fixed interval. This he called "fixed" virus. Because dogs sometimes developed rabies following subcutaneous inoculation with the fixed virus he attempted further to alter the virus by drying. The method employed was to suspend the spinal cord of a rabbit killed when prostrate with fixed virus rabies in a sterile jar containing sticks of potassium hydroxide. The virulence of cords so treated gradually diminished so that after 7 to 10 days exposure they were no longer infectious. A series of about 100 dogs were immunized by the daily administration of suspensions of dried cord beginning with those dried 14 days and each subsequent day using cord dried for a shorter period until fresh cord was given. The dogs so treated did not contract rabies from the treatment and subsequently were immune to experimental inoculation with virus obtained from naturally infected dogs which Pasteur called "street" virus. The French Academy of Science became interested in this method of immunization and appointed a committee to investigate the work of Pasteur. It was recognized subsequently as an extremely important discovery.

Pasteur then began a series of studies in which the same type of treatment was given to dogs following exposure to rabies. The results of these studies are not clear from the published data but Pasteur evidently obtained results which convinced him that the disease could be prevented by such a course of treatment. Before these studies had been confirmed

Etiology

Nature of the Virus

The causative agent of rabies is an ultramicroscopic filterable virus The size of the individual infectious unit has been estimated at 100 to 150 millimicrons (Elford) This figure was obtained by filtration of rabies fixed virus through graded collodion membranes Rabies virus is not readily filterable The virus passes the V grade Berkefeld filter fairly well but the finer N and W type filters withhold the virus the former allowing partial filtration and the latter little or none It is seldom possible to obtain any virus in the filtrate where the Seitz number I serum sterilizing filter is used even with cell free suspensions of high titre The difficulty in filtration may be due in part to adsorption of the virus in the filter

Resistance of Virus to Physical and Chemical Agents

The virulence of infected brain tissue if exposed to air is rapidly lost The original Pasteur rabies vaccine treatment depended on a gradual decrease in the virulence of spinal cords of infected rabbits dried for varying periods of time at room temperature

The loss of virulence due to exposure to air must be largely due to hydrolysis and oxidation as with modern methods of quick freezing and drying at sub freezing temperature under vacuum a completely dry preparation of high virulence is obtainable When the sealed ampoules are stored at −25 C there is no significant alteration in titre over a period of several months

Rabies virus is very sensitive to sunlight or artificially produced ultraviolet light Sunlight will inactivate virus suspensions in a few hours Ultraviolet light irradiation will inactivate concentrated virus suspensions in 10 to 30 minutes

Water suspensions of rabies virus are destroyed readily by heat Suspensions of fixed virus usually are inactivated in 4 to 5 days at 37° C A temperature of 45 C will inactivate concentrated fixed virus suspensions in 24 hours 50 C in one hour 52 to 58° C in thirty minutes 60° C in five minutes and 100 C in two minutes

Distilled water is the best diluent for rabies virus as normal saline or other isotonic chemical solutions exert a deleterious action on the virus If 10 per cent serum is added to the distilled water the virus survives still longer

again advocated the dilution method for human vaccination. He began the treatment with highly diluted noninfectious suspensions of fresh infected rabbit cord material, increasing the concentration in graded doses and finishing the course with a 1 to 100 suspension.

Fermi in 1908 was the first to use a chemical inactivating agent for preparing human rabies vaccine. He introduced a phenol inactivated fixed virus vaccine which, after modification by Semple in 1911, has largely supplanted other vaccines. Formalin inactivated vaccines have been recommended by Cumming and van Stockum, and ether treated vaccines by Remlinger, Alivisatos and Hempt. The heat inactivated vaccine of Babes and the serum virus vaccines of Fermi and Marie have been used also on a considerable scale. The chloroform treated vaccine of Kelser has not been extensively used for the treatment of man.

Harris and Sellers are among the later advocates of live virus vaccines. There are no clear cut experimental studies proving the superiority of any one type of vaccine; consequently most of the vaccines mentioned above are in use at one place or another.

Though Virchow, Golgi, Babes and other early pathologists presented accurate histological studies of the pathology of rabies, except for the description of the rather characteristic but nonspecific perivascular and perineuronal cellular infiltration no practical microscopical method for the diagnosis of rabies was found. In 1903 Adelchi Negri described the occurrence of specific intracytoplasmic inclusion bodies in the nerve cells of man and animals which had died of rabies. Despite his failure to recognize the role of these structures, the discovery of Negri proved to be very important, as it made possible the rapid microscopical diagnosis of rabies.

Hoyt and Jungeblut (1934) made an important contribution to the knowledge of rabies when they demonstrated that intracerebral inoculation of mice with rabies virus consistently produced infection with a short and relatively constant incubation period. Webster and Dawson subsequently demonstrated the practicality of using the mouse for diagnostic animal inoculation and serum neutralization tests.

Kanazawa and Webster and Clow were the first workers to cultivate rabies virus in vitro. Rabies virus grown in tissue culture has not as yet proved to be a practical source for making vaccine. Untreated tissue culture virus has not been used for immunization because of its high pathogenicity for experimental animals when inoculated intracerebrally. Neither has it been possible to prepare a chemically or physically inactivated vaccine from tissue culture virus that compares in potency with vaccines made from infected animal brain.

order is increasingly efficacious in producing the disease Intracerebral inoculation of concentrated virus suspensions is practically always fatal

Ducks geese doves and chickens are susceptible but relatively refractory Young birds in general are susceptible to intracerebral inoculation but the incubation period is prolonged Recovery from rabies is relatively frequent in adult chickens Buzzards are more susceptible than chickens and may be infected by intranasal inoculation Cold blooded animals are very refractory

Mode of Transmission of Virus

Transmission of the disease depends on the ability of the virus to reach and to multiply in the salivary glands of a rabid animal The virus then is excreted with the saliva Generally it is necessary for the animal to become vicious and bite so that the virus will be implanted in a fresh wound in order to transmit the disease The exceptions are found in the vampire bat which inflicts a wound in order to feed and in cases in which persons are exposed by attempting to treat animals ill with paralytic rabies

The question arises whether the saliva is infectious before the onset of symptoms Some writers report finding the virus in the saliva several days before the onset of symptoms It is probable that they refer to the classical stage of the disease It is unlikely that the virus is present in the saliva before the development of prodromal symptoms At this stage however the animal may appear quite normal

The saliva probably functions in a two-fold manner (1) to preserve the virus by the protective action of the mucus and (2) to act on the exposed tissue possibly by some digestive action to assist the entry of the virus into the nerves

There is still some doubt as to whether the virus reaches the central nervous system by way of the axons or the perineural lymphatics but the former route appears more likely The symptomatology and pathology indicate that the virus travels predominantly by way of the sensory nerves The ability to infect animals by means of a slight scratch on the cornea or skin supports this theory The blood stream and lymphatics do not appear to play any significant part in the invasion or propagation of the virus

Distribution of the Virus in the Body

The virus is almost always demonstrable in the central nervous system of man and animals dying of rabies The possible exception is found when

One of the peculiarities of rabies virus is its resistance to the action of phenol. Saline suspensions of infected rabbit brain containing 0.5 per cent phenol remain infectious for periods up to two months when stored in an ordinary refrigerator. Pure glycerin has little harmful effect on the virus but does inactivate bacteria, which makes it an excellent medium for preserving infected brain material. If stored in pure glycerin animal brains infected with rabies virus remain virulent for several weeks at room temperature. Similar material stored in an ordinary refrigerator will be virulent for at least one year.

Bichloride of mercury, formalin and strong acids rapidly destroy the virus. Nitric acid is used widely in the treatment of wounds inflicted by rabid animals because of its rapid destruction of the virus. Bile, pancreatic lipase and 1 per cent hydrochloric acid inactivate the virus. Trypsin and diastase are less effective in destroying the virus.

Cultural Characteristics of Virus

It has not been possible to cultivate the virus on ordinary bacteriological media. Multiplication takes place only in the presence of living cells. Continued growth is possible in tissue culture with a medium of Tyrode's glucosol or saline solution containing 5 to 10 per cent human or monkey serum and a small amount of finely minced mouse embryo brain. The virus may be maintained indefinitely in this manner. To date it has not been possible to obtain a high yield of virus in tissue culture, nor has there been a report of any significant decrease in the pathogenicity of the culture virus either for man or for the canine species.

The virus does not multiply in the chorioallantoic membrane of the developing chick embryo, but serial passage in chick embryo is possible when the virus is inoculated into the embryo brain.

Toxic Products of Virus

No soluble toxin has been isolated from tissue virus suspensions or tissue culture material.

Pathogenicity of Virus

Rabies virus is pathogenic for all warm blooded animals. Infection does not take place through the intact skin or by ingestion, but the dog and mouse often will develop the disease if the virus is instilled into the nose. It is difficult to infect animals by subcutaneous or intraperitoneal inoculation, but injection into the skin, muscle or nervous tissue in that

disease course produced Such virus strains have largely lost their tropism for organs other than the brain

Street Virus — There are a number of reports in the literature of unusual strains of rabies street virus Most of these accounts concern virus strains isolated from human or animal rabies cases in which the recovered virus has certain characteristics of fixed virus The species specificity of rabies street virus may be altered by passage through certain animal hosts This probably accounts for the atypical character of the oulou fato rabies of French West Africa and the vampire bat rabies of South America Street virus rabies ordinarily is characterized by a long and extremely variable incubation period and the rather constant production of inclusion bodies in the brain By intracerebral inoculation the incubation period in rabbits usually is from 12 to 15 days with a range of from 10 to 90 days Street virus rabies often results in a prolonged excitement stage with irritability and viciousness In a variable but high percentage of cases the virus is able to reach the salivary glands and be excreted in the saliva

Natural Resistance to Rabies Virus

Man appears to have some natural resistance to infection with rabies virus The pathogenicity of the virus for man is altered by passage in certain animals such as the rabbit The resistance to infection seems to increase with age There is no satisfactory explanation for the occasional occurrence in the blood of man or animals of a high concentration of virus neutralizing substance not preceded by vaccination or known exposure to the virus

Acquired Immunity to Rabies

Pasteur demonstrated that if fixed virus is inoculated subcutaneously into dogs infection is rarely produced and that if repeated injections are given the animals subsequently become highly resistant to experimental infection Early investigators also found that the intraperitoneal injection of large amounts of virus produced a high degree of immunity There appears to be a quantitative relationship between the amount of virus given and the degree of immunity produced The blood serum of animals so treated has a uniformly high content of virus neutralizing substance Immunity may be produced also by the injection of vaccines prepared from infected brain tissue treated by certain chemical agents so as to render the virus inactive The duration of immunity acquired by vaccination has not been determined

the disease is prolonged The concentration of the virus varies in the different parts of the brain but usually it is high in the thalamus and medulla The virus content of the cerebral cortex is subject to great variation in naturally infected animals This may account for the variable clinical pattern of the disease The maximum concentration of virus occurs during the early acute phase of the disease then decreases gradually in amount There is no satisfactory evidence to prove that the virus enters the blood stream during the incubation period or at any time during the course of the disease The spinal fluid rarely contains any virus

Rabies virus is not strictly neurotropic The submaxillary glands are the best source of virus aside from the central nervous system and the concentration of the virus in this gland is often as high as that in the brain The histopathological changes in these glands indicate that the virus has an especial affinity for the mucus secreting cells In a series of dogs experimentally infected by injection of street virus in the masseter muscles, the submaxillary gland was positive for virus in 39 of 67 animals 58 per cent The percentage of positive glands varied with different strains of test virus The parotid gland was positive in 4 of 47 dogs 9 per cent and the lacrimal gland in 12 of 33 dogs 33 per cent The adrenal glands often contained the virus The pancreas and kidney were invaded in rare instances by the virus In one of four lactating dogs the virus was found in the breast tissue Numerous tests of whole blood and bone marrow spleen liver lymph nodes ovary testes prostate rectal glands and the mucosa of the appendix and of the small and large intestines have been consistently negative

Virus Strains

There is no satisfactory evidence to indicate that there are antigenically different strains of rabies virus Variation in street virus strains has received much attention since first advanced by Pasteur The major difference in virus strains concerns the alteration of the virus by intracerebral passage in animals

Fixed Virus — This term is applied to virus strains that have been propagated by serial intracerebral passage in some experimental animal usually the rabbit and the incubation period has reached a minimum 'fixed interval Fixed virus rabies is characterized by a short incubation period usually 4 to 6 days after intracerebral inoculation absence of typical inclusion bodies wide dissemination in the central nervous system with consequent high titre and by the uniformly rapid and paralytic

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Immunological Tests

It is necessary sometimes to resort to special tests in order to identify atypical strains of rabies virus especially those modified by intracerebral passage This may be accomplished either by determining whether the virus is neutralized by a known immune serum or by vaccinating animals with a known strain of rabies virus and testing them with the virus in question in parallel with an equal number of control animals

Canine Rabies

Rabies is primarily a disease of the canine species i e the dog, wolf, coyote and jackal The disease is perpetuated easily in such hosts because of the instinctive fighting and biting nature of such animals With the development of rabies they often become extremely aggressive against their own kind as well as against any living thing they meet The potentially long incubation period allows survival of the virus from year to year through the medium of only a few animals In an area in which any one of these species becomes unduly abundant rabies may become epizootic but for the most part the disease maintains a low incidence The general disease picture of canine rabies is best illustrated by the course of the disease in dogs

The incubation period for naturally infected dogs is rarely under 10 or over 90 days In most instances the disease will develop between the twenty first and sixtieth day after exposure Latent periods of over 200 days have in rare instances been noted in this country and European writers have reported incubation periods of over one year

The early symptoms include congestion of the mucous membranes of the eyes and nose The temperature of the body generally is elevated one to two degrees above normal The animal exhibits either depression or excitation depending on the manner in which the body reacts to the infection When the depressive phase is predominant the animal is morose and seeks seclusion Where the excitation phase is predominant, the dog will be unusually active, playful and friendly There will be a tendency to fawning and licking The ears tend to point producing an alert appearance A certain degree of restlessness and irritability is present so that slight provocation may cause the animal to bite The normal tendency to chase cats and chickens is increased At this period of the disease the animal is very dangerous to children as they are apt to pick up and fondle the apparently affectionate dog

Two general types of canine rabies are described the one is called furious and the other dumb or paralytic rabies In the latter the paralytic phase develops early and is associated with depression and apathy The majority of cases show some manifestation of both types of the disease i e a short excitation phase characterized by restlessness and *nervousness rapidly followed by depression and paralysis* Sudden death without appreciable premonitory symptoms may occur The incidence of furious versus dumb rabies is not constant but depends on the virulence of the virus and the species of animal affected

Furious Rabies

This is the type where the classical mad dog symptoms appear Dogs so affected become increasingly restless and are easily startled There is usually some weakness of the vocal cords which produces a characteristic voice change A hoarse howl like bark is followed by a succession of *baying barks of lower pitch The maximum pitch is attained* in the middle of the bark rather than at the beginning The appetite is perverted and there is a desire for undigestible material such as sticks straw dirt etc Priapism and sexual excitation are common The eyes present a peculiar appearance because of the congestion of the conjunctivæ dilation of the pupils and difficulty in closing the eyes The cornea become dry and glazed due to infrequent blinking The animal becomes *increasingly apprehensive*

If caged the dog will make every effort to escape even breaking off the teeth in an effort to chew its way out If free the animal often will leave home to wander for miles and seems impelled to attack any living thing that it sees There seems to be little desire to kill and if several animals are present the dog will attack first one and then another A dog so affected may travel a long distance before succumbing to paralysis and exhaustion *More often the animal returns home after one or two days absence emaciated* wounded and almost unable to walk because of incoordination and beginning paralysis Salivation of some degree generally is present but in the terminal stage the mouth often becomes dry and parched

The dog with furious rabies may have some weakness of the jaw but usually can close the mouth and drink and eat In some instances the dog will die suddenly perhaps in a convulsion More often the animal will develop *paralysis The legs become gradually weaker the jaw droops* and death occurs after the development of coma Dogs with this type of the disease usually live 4 to 7 days but may live as long as 10 days after the onset of symptoms

Dumb or Paralytic Rabies

In this type of the disease the excitation phase is short or absent and the animal rarely will attempt to bite even if provoked to do so The early symptoms of depression and apathy soon are followed by paralysis of the jaw and muscles of deglutition Salivation usually is profuse thick stringy saliva drooling from the open mouth The difficulty in swallowing causes choking, gagging and retching The dog is unable to bark hence the name dumb rabies Paralysis of the extremities develops rapidly and is associated with marked incoordination due to the spastic character of the paralysis The dog soon is prostrated and comatose lying on its side the legs moving rhythmically back and forth The eyes are wide open and the corneæ soon become glazed and opaque Respirations are slow and irregular Death usually occurs in 1 to 3 days rarely over 5 days after the onset of symptoms

All dogs with rabies are relatively insensible to pain They do not fear blows or threats Dogs with furious rabies may mutilate themselves biting out large pieces of skin and muscle without apparent pain An early symptom referable to sensory paralysis is the loss of the corneal reflex The excitation of muscles causes tic like contractions, tremor and occasionally general convulsive seizures The muscular reflexes are increased Trismus of the jaw may occur There is no definite pattern of muscular paralysis The weakness may begin in one or both of the front or hind extremities and progressively involve other muscles There is no fear of water such as occurs in human rabies The body temperature usually is subnormal during the greater part of the disease A high terminal temperature may occur The disease is practically always fatal to the dog

Rabid wolves and foxes lose their normal fear of human beings and human habitation and will fearlessly invade farm premises and attack man and domestic animals Wild animals with paralytic rabies are found rarely Animals so affected probably die in seclusion avoiding even their own species

Possible Carrier State

There are numerous reports in the literature of persons dying of rabies following the bite of a dog that did not appear abnormal or later die of rabies This is suggestive of a possible *carrier state* It is probable that the history in such cases was incomplete and more than one in

stance of exposure to rabid animals had occurred or the identity of the biting dog was not definitely established

The only proved instance of recovery from rabies in dogs is the case described by Remlinger He observed an experimentally infected dog that presented symptoms of rabies for a period of three weeks and subsequently recovered The virus was recovered from the saliva of the animal during the symptomatic stage and up to five days after the cessation of symptoms

The author has observed several hundred dogs experimentally inoculated with rabies virus In rare instances a dog would exhibit transient excitation apathy incoordination or muscular weakness at some time during the three month period of observation In no instance was it possible to demonstrate rabies virus in the saliva of these animals When such animals were killed three months after the virus inoculation the salivary glands were tested for rabies virus by intracerebral inoculation of mice with a suspension of the gland material These tests were consistently negative There was no instance of a dog developing characteristic symptoms of furious rabies followed by recovery

It is the author's opinion that dogs in rare instances may develop an abortive type of rabies and recover It is extremely unlikely that the animals so affected will have the virus in the salivary glands. There is at present no evidence to indicate that the dog can act as a symptomless carrier of rabies such as may occur in vampire bats

Vampire Bat Rabies

The vampire bat was not recognized as a vector of rabies until 1916 when Rehaag succeeded in infecting laboratory animals with brain material from a bat captured while feeding on a cow An unidentified paralytic disease had caused great loss of livestock in Brazil as early as 1906 In 1911 Carini demonstrated inclusion bodies in the brains of cattle dying of ascending paralysis in the Sao Paulo district of Brazil He concluded that the disease was rabies but quarantine and destruction of dogs and cats did not affect the spread of the disease In 1921 Haupt and Rehaag proved that the atypical livestock disease was rabies and came to the conclusion that the vampire bat was the principal source of the infection A severe epizootic of rabies in cattle began in 1931 in the states of Matto Grosso and Santa Catarina Brazil Torres and de Queiroz Lima captured several vampire bats in an area where the disease was prevalent and several of these bats proved to be carriers of rabies These men later proved that bats could harbor the virus in the salivary

glands for as long as 110 days and still remain symptomless Experimentally infected bats sometimes developed paralytic symptoms and died after long periods of infectiousness The incubation period following experimental inoculation varied from 7 to 171 days Some bats failed to develop the disease

Torres and de Queiroz Lima sometimes found that captured bats had the virus in the salivary glands but not in the brain De Verteuil and Urich later reported that one experimentally infected bat remained a carrier for 5 months The species specificity of the virus appears to have been altered by passage through bats Dogs were found to be only slightly susceptible to this strain of virus Though rabbits and guinea pigs were susceptible to infection rats had a low susceptibility even though inoculated intracerebrally

The vampire bat is a normal inhabitant of a large part of Central and South America The animal is relatively small having a body length of four inches and a wing spread of thirteen inches It subsists entirely on fresh blood which it laps up after inflicting a superficial crater like wound with its sharp incisor teeth Its saliva contains an anticoagulant which causes prolonged and profuse bleeding from relatively minor wounds These animals live in caves or hollow trees and normally feed only at night Their favorite hosts are cattle horses and chickens but where the livestock is protected at night they will enter homes and feed on man Their ability to bite and feed without awakening the victim is legendary

The fruit eating bats form an additional reservoir of rabies for although they do not transmit the disease to man and animal they can perpetuate the disease in the bat species

In 1929 a severe epizootic of cattle rabies began in Trinidad British West Indies Hurst and Pawan showed that the disease was introduced and transmitted by vampire bats From 1929 to 1935 there were 55 cases of human rabies in Trinidad as the result of infection from bats

The disease in man was paralytic in type and the classical hydrophobia symptom was encountered rarely The duration of the disease was relatively longer than usual for human rabies One patient lived for 30 days after the onset of symptoms The first symptom usually was some abnormal sensation about the site of infection This was followed by gradual ascending paralysis

Iturbe and Gallo reported the presence of vampire bat rabies in Venezuela It has been reported also in Paraguay Argentina and British Guinea

Rabies in Man

Incubation Period

The incubation period averages 42 days Rabies may develop as early as 10 days after exposure Incubation periods of over 90 days are relatively rare Hogyes in 1886 reviewed the histories of 210 cases of human rabies Of these 88 per cent had an incubation period of less than 90 days with 65 per cent under 60 days He included one case with a latent period of 646 days The records of 137 cases of human rabies have been collected by the author The average incubation period was 42 days with a range of from 12 to 210 days

There is no good evidence to support the hypothesis that the incubation period depends on the distance the virus has to travel from the point of infection to reach the brain In the author s series two patients bitten on the face had incubation periods of 63 and 146 days respectively The average incubation period was 30 days for the 44 persons bitten on the head 50 days for the 56 persons bitten on the upper extremities and 44 days for the 12 people bitten on the leg Experimental studies show that the amount of virus introduced and the type of tissue exposed influence the duration of the latent period In all experimental animals the inoculation of a concentrated virus suspension results in a shorter average incubation than when dilute virus is given Long latent periods are frequent when street virus is introduced into the skin of the face and incubation periods up to 90 days are noted occasionally in dogs inoculated in the masseter muscle or in the brain It is therefore evident that the incubation period is largely dependent on a temporary arrest of virus multiplication either at the site of infection or at some place in the nervous system

The relatively high morbidity and short average incubation period of rabies following face exposure may be accounted for by the frequent severe laceration in such exposures the superficial aspect of the muscle tissue and the abundant sensory innervation of the face Then too there is a tendency not to use nitric acid for cauterizing face wounds for fear of disfigurement

There is no satisfactory proof that the average incubation period is shortened or lengthened by the rabies vaccine treatment

Other factors said to influence the incubation period include the virulence of the virus the species of biting animal and the age of the exposed individual The average incubation period for children developing rabies is shorter than that of adults

glands for as long as 110 days and still remain symptomless Experimentally infected bats sometimes developed paralytic symptoms and died after long periods of infectiousness The incubation period following experimental inoculation varied from 7 to 171 days Some bats failed to develop the disease

Torres and de Queiroz Lima sometimes found that captured bats had the virus in the salivary glands but not in the brain De Vertueil and Urich later reported that one experimentally infected bat remained a carrier for 5 months The species specificity of the virus appears to have been altered by passage through bats Dogs were found to be only slightly susceptible to this strain of virus Though rabbits and guinea pigs were susceptible to infection rats had a low susceptibility even though inoculated intracerebrally

The vampire bat is a normal inhabitant of a large part of Central and South America The animal is relatively small having a body length of four inches and a wing spread of thirteen inches It subsists entirely on fresh blood which it laps up after inflicting a superficial crater like wound with its sharp incisor teeth Its saliva contains an anticoagulant which causes prolonged and profuse bleeding from relatively minor wounds These animals live in caves or hollow trees and normally feed only at night Their favorite hosts are cattle horses and chickens but where the livestock is protected at night they will enter homes and feed on man Their ability to bite and feed without awakening the victim is legendary

The fruit eating bats form an additional reservoir of rabies for although they do not transmit the disease to man and animal they can perpetuate the disease in the bat species

In 1929 a severe epizootic of cattle rabies began in Trinidad, British West Indies Hurst and Pawan showed that the disease was introduced and transmitted by vampire bats From 1929 to 1935 there were 55 cases of human rabies in Trinidad as the result of infection from bats

The disease in man was paralytic in type and the classical hydrophobia symptom was encountered rarely The duration of the disease was relatively longer than usual for human rabies One patient lived for 30 days after the onset of symptoms The first symptom usually was some abnormal sensation about the site of infection This was followed by gradual ascending paralysis

Iturbe and Gallo reported the presence of vampire bat rabies in Venezuela It has been reported also in Paraguay, Argentina and British Guinea

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Prodromal Symptoms

Prodomata last 2 to 4 days General symptoms such as headache anorexia nausea and sore throat often are present Lacrimation and a watery nasal discharge may occur early in the disease Headache, when it occurs most often is localized in the occipital region or over the vertex Vomiting may be protracted or even projectile in character The patient often complains of fever but this symptom is out of proportion to the degree of elevation of the body temperature which may be normal or elevated one to three degrees Respirations may be shallow with an occasional deep inspiration The patient while speaking may be in terrupted by a sighing inspiration The pulse rate usually is increased and is more rapid than would be expected in proportion to the degree of fever The patient may complain of a dry throat and extreme thirst but will drink very little at a time or not at all

Nervousness irritability anxiety melancholia apathy and depression are common manifestations Insomnia or interrupted sleep gives evi dence of the stimulation of the central nervous system The patient may wake up suddenly as if suffering from bad dreams

The most diagnostic early symptom of rabies is some abnormal sensation about the site of infection This will occur in about 80 per cent of the cases and when present is substantial evidence for a diagno sis of rabies There may be pain burning sensation of cold pruritus tingling or formication about the old wound The pain may be local or radiating Pain along the affected nerves may be dull and constant or intermittent and stabbing in character Referred pain in the neck, back chest or abdomen has been noted occasionally Local numbness of the skin about the old wound is often present It is probable that the inflam mation of the old wound so often described in rabies is secondary to scratch ing or rubbing due to the abnormal cutaneous sensations It is also possible that some sort of urticarial or angioneurotic like skin reaction may occur

In general the early symptoms can be ascribed to the stimulative action of the virus on various groups of brain cells predominantly af fecting the sensory system In addition to symptoms of this nature already mentioned there may be general hyperesthesia of the skin and sensitivity to drafts and bed clothes

Acute Phase of Rabies in Man

The symptoms noted in the prodromal stage become more prominent For the most part the excitation phase is predominant up to death The

patient is extremely nervous, apprehensive and extraordinarily sensitive to all types of physical stimuli. Often he will be able to be up, wandering aimlessly about and speaking in disconnected sentences, and may suffer from intermittent spells of delirium. Maniacal seizures may occur, but vicious and murderous action, such as biting and fighting, is infrequent. In general the patient is well oriented and will answer questions in an intelligent fashion.

A sense of impending death is frequent. The eyes are bright and starry and seldom fix on any object. Despite the great fear and anxiety there are no tears. There is usually an accumulation of thick, tenacious mucus in the throat and mouth, and in an effort to expel it the patient emits a harsh coughing sound which sometimes has been interpreted as a bark.

The outstanding clinical symptom is related to the act of swallowing. On attempting to drink, when the fluid comes in contact with the fauces, it is expelled with considerable violence, and painful contractions of the muscles of deglutition and of the accessory muscles of respiration are produced. This is so classical when present that the disease has been called hydrophobia, the fear of water. The fear of swallowing is not related to water alone but to any fluid, food or medicine. Choking when attempting to swallow saliva or fluids may occur, and convulsive seizures often are precipitated under this stimulus. The choking may result in such spasm of the respiratory muscles that prolonged apnea occurs with concomitant cyanosis and gasping attempts at respiration. Due to the inability to take fluids there is excessive thirst and progressive dehydration. The voice is apt to be hoarse. There is excessive reaction to external physical stimuli, such as noise, drafts, bed coverings and bright light.

The entire muscular system is activated, and tic-like vermiform and fibrillar muscular contraction and general tremors may occur. Convulsive seizures are common and may be so extreme as to produce opisthotonos. The convulsive seizures usually are of short duration and are apt to recur in a cyclical rhythm. There is usually some ataxia.

In the majority of instances the patient will die in the early acute phase of the disease during a convulsive seizure. Therefore the paralytic phase due to degeneration of motor nerve cells is usually not very evident. However, weakness of muscle groups related to the site of exposure is present in about 25 per cent of human rabies cases. Ocular palsies leading to strabismus and incoordination of ocular muscles may occur. Weakness of the masseter and facial muscles may be present in some of the patients.

Paralytic Phase

When the acute phase of the disease is prolonged more than three days paralysis of various muscle groups is the rule There is then increasing paralysis of the muscle group related to the site of exposure if previously affected and subsequent development of weakness in the contralateral musculature This extends until death occurs from respiratory paralysis or cardiac arrest

In rare instances the paralytic type of the disease takes on the ascending pattern such as occurs in Landry s syndrome and beginning with the muscles of the legs a progressive ascending paralysis occurs with no relation to the site of exposure Patients so affected may have no difficulty in swallowing until the terminal phase of the disease

The affection of the general visceral efferent nervous system leads to a variety of symptoms The eyes may exhibit a variety of signs due to overstimulation of one or the other types of innervation The salivation often noted does not necessarily mean increased secretion but rather, inability to swallow saliva leading to drooling The mucous membranes in general are dry owing to decreased secretion so that the eyes become glassy and the throat and nasal passages become dry and irritated There is often abnormal stimulation of the innervation of the sex organs with resultant priapism and increased libido The bladder and rectum are affected so that retention and constipation are the rule though incontinence may occur especially if the disease is prolonged

Objective Symptomatology

Due to dehydration and marked apprehension the facies present a wild fearful and gaunt appearance The eyes are sunken and the corneæ are glazed and reflect the light The circumocular muscles may be weak so the patient cannot completely close the eyes The skin is increased in turgor and the normal elasticity is diminished The conjunctival and mucous membranes elsewhere are dry and congested

Though there may be stiffness of the neck Kernig s and Brudzinski s signs usually are not elicited Tenderness over the spine may be present The corneal reflex is decreased or absent The pupils usually are widely dilated but may be constricted or unequal Hippus nystagmus diplopia or strabismus may occur The retina is usually normal in appearance but partial blindness is not uncommon

The respirations are shallow and irregular with occasional forced inspiration or sighing expiration Cheyne Stokes type of respiration is noted often The pulse rate usually is rapid and the volume shallow Bradycardia may be encountered in rare instances

The chest and abdomen usually are normal to palpation and auscultation Local involuntary muscle activity may be noted The superficial reflexes of the abdominal musculature may be absent normal or increased The tendon reflexes are increased during the early stages and disappear where the disease is prolonged The muscular paralysis usually is flaccid in type

Though the skin in general is hyperesthetic local sensation to pin prick heat and cold is diminished The body temperature may be normal subnormal or slightly increased There is rarely high fever except in occasional instances in the terminal stage of the disease

Clinical Pathology

Blood — The red blood cell count is not altered in rabies except where excessive dehydration occurs and the blood is concentrated The white blood cell count generally is increased and may reach 20 000 to 30 000 Blood smears are apt to show a relative increase in the percentage of polymorphonuclear and large mononuclear cell types

Urine — A slight albuminuria frequently is present and hyaline casts may be seen in the urine sediment A reaction for glucose is noted often

Spinal Fluid — There is no marked increase in the spinal fluid pressure but the level usually will be above normal The fluid is consistently clear Protein tests may show a slight positive reaction The cell count usually is normal Cell counts of from 25 to 150 are encountered in rare instances Where the cell count is increased the cells are predominantly of the mononuclear type The spinal fluid rarely contains any virus

Differential Clinical Diagnosis

If the patient is known to have been bitten by a rabid animal and the symptomatology is characteristic there is no difficulty in making a correct clinical diagnosis However in some instances it is impossible to obtain a history of exposure to a rabid animal In such cases should the clinical course be atypical the differential diagnosis may prove difficult

Treatment Paralysis — This may be one of the most difficult diseases

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Pathology

Gross Pathology

There are no gross abnormalities which can be regarded as diagnostic of rabies. The macroscopical changes produced by the virus of rabies are similar to those resulting from a variety of bacterial, rickettsial and virus infections and from toxic or allergic reactions. Rabies produces rapid dehydration and at death the body presents a cachectic appearance.

The meninges are normal except for vascular congestion and the spinal fluid is clear and colorless. The surface of the brain and cord usually exhibits a pink or red discoloration due to marked engorgement of the blood vessels. There is slight to moderate cerebral edema as shown by flattening of the cerebral convolutions and partial obliteration of the sulci. On section the cut surface of the brain and cord has a pink cast due to vascular congestion. Usually this is most marked in the thalamus, medulla and cervical spinal cord. Perivascular hemorrhage is rarely evident on gross examination. When the site of exposure was located on one of the extremities the cut surface of the cord sometimes will show unilateral pinkish gray discoloration and obliteration of the normal markings. This lesion when present is most marked in the posterior horn area.

The lungs usually show some pulmonary edema and focal atelectasis and the mucosa of the trachea and bronchi is congested. The thymus gland may be edematous and congested. The small intestine sometimes presents the picture of paralytic ileus. The mucous membrane of the gastrointestinal tract is congested. Local digestion of the gastric mucosa with perforation of the stomach and diaphragm and the presence of stomach contents in the pleural cavities is a frequent finding. The viscera otherwise are quite normal in appearance.

Microscopical Pathology

Central Nervous System. — The meninges usually are normal. A variable degree of hyperemia and slight perivascular infiltration with *mononuclear cells may be seen. The cerebral and cerebellar cortex* and adjacent white matter show no significant alteration other than hyperemia and acute neuronal degeneration. In the midbrain, basal ganglia and pons the neuronal degeneration generally is severe and is associated with marked hyperemia. Small perivascular hemorrhages are seen frequently. These are most noticeable in the thalamus and subependymal neuroglial tissue. Neuronal degeneration is especially severe in the thalamus, hypo

to distinguish from rabies The course may be clinically very similar to the paralytic type of rabies It is important to ascertain whether the patient had any systemic reaction to the vaccine treatment The excitation phase so characteristic of rabies is absent The spinal fluid cell count is of little aid in the diagnosis as it is only slightly increased but xanthochromia usually is present in treatment paralysis cases

Hysteria — This diagnosis should be considered always as it is encountered frequently The nature of the convulsive like seizures should make the diagnosis evident The patient often will try to emulate a mad dog

Poliomyelitis — Both the bulbar and spinal type of this disease may be confused with rabies The spinal fluid cell count in poliomyelitis usually is higher than that in rabies and the relative absence of polymorphonuclear cells in the latter disease may help to differentiate the two

Tetanus — The incubation period of tetanus is shorter than that of rabies usually 6 to 14 days and the psyche is normal Trismus of the jaw though a very constant symptom of tetanus is rarely present in rabies The muscular spasticity in tetanus is constant and general while in rabies it is intermittent and chiefly restricted to the muscles of the throat

Prognosis and Treatment

There are a few reports in the literature of rabies in man followed by recovery but these are questionable as the virus in no instance was isolated Rabies in man as far as known is invariably fatal

A variety of chemicals have been used in an attempt to cure rabies At the present time there is no medicinal known which will alter the course of the disease The use of hyperimmune serum has been recommended but here again there has been no evidence that it has had any curative effect Though intravenous administration of fluids might prolong the disease and will relieve the dehydration it has not resulted in recovery The main treatment has consisted of the administration of strong sedatives to relieve the anxiety and the administration of anesthetic drugs to stop the convulsions

Though morphine is the choice of drugs for relieving the symptoms of rabies the marked resistance to the drug exhibited by persons so afflicted requires that large doses be given Even gr 1 (60 mgm) of morphine given subcutaneously often fails to quiet the patient Phenobarbital sodium given subcutaneously or intravenously also is an excellent sedative



FIG. 2. (top) Routine diagnostic impression preparation of the Ammon's horn of a dog dying of furious rabies. Seller's stain; magnification 250. Photograph by J. B. Haulenbeck.

FIG. 3. Paraffin section of the Ammon's horn of a dog experimentally infected with rabies; modified Mosin methylene blue stain; magnification 1,000. Photograph by J. B. Haulenbeck.

thalamus substantia nigra and the cranial nerve nuclei These areas show a slight perivascular and perineuronal mononuclear cell infiltration The medulla uniformly presents the maximum pathological alteration The cranial nerve nuclei exhibit marked neuronophagia and the inflammatory cellular infiltration is proportionally greater than elsewhere

The spinal cord shows hyperemia and perivascular cellular infiltration These findings are especially marked in the cervical portion at the decussation of the motor tracts Neuronal degeneration is general but the posterior horns of the gray matter are affected especially severely When the site of exposure is located on one of the extremities the corresponding posterior horn area is apt to show marked hyperemia and cellular infiltration Small hemorrhages may be present The tracts of Goll and Burdach and the posterior funiculus may show marked degeneration of axons and myelin sheaths

In general the leucocytic infiltration is largely perivascular but clusters of mononuclear cells are found about degenerating neurons especially in the cranial nerve nuclei The infiltrating cells are for the most part of the small and large lymphocyte type There is usually a slight diffuse mononuclear cell infiltration of the interstitial tissue of the pons medulla and cervical spinal cord varying in proportion to the degree of neuronophagia Relatively few polymorphonuclear cells are seen A few mast cells usually are found in the medulla Cellular infiltration is more marked when the disease has been of longer duration

The neuroglial cells of the substantia gelatinosa about the central canal show a variable degree of proliferation This is especially evident in the spinal cord The neuroglia about degenerating neurons becomes more prominent than is normal This is probably in part a functional increase in size but where the degeneration is heavy there appears to be some actual proliferation The oligodendroglia throughout the brain show swelling which is evidently a manifestation of the moderate cerebral edema which is regularly present

The major proportion of the neurons of the central nervous system shows some pathological alteration The main change consists of pyknosis of the nucleus and ballooning of the cytoplasm The Nissl substance is decreased in amount and the cytoplasm exhibits variable vacuolization and granular and fatty degeneration Some neurons show condensation of the cytoplasm presenting a coagulative type of necrosis Other neurons exhibit fragmentation of the cytoplasm and general loss of cell detail

Inclusion Bodies —The inclusion bodies which frequently occur in the neurons of both man and animals dying of rabies generally are referred to as "Negri bodies (Figs 2 and 3) These structures usually



FIG. (top) Routine diagnostic impression preparation of the Ammon's horn of a dog dying of furious rabies. Sellers stain, magnification 50, photograph by J. B. Haulenbeck.

FIG. 3. Paraffin section of the Ammon's horn of a dog experimentally infected with rabies, modified eosin methylene blue stain, magnification 1,000, photograph by J. B. Haulenbeck.

are very characteristic and if they are demonstrable it is possible to make a definite diagnosis of rabies The inclusion bodies are found in the cytoplasm of large neurons which present the ballooning type of degeneration They consist of sharply defined spherical oval or elongated eosinophilic staining bodies varying from 1 to 30 micra in diameter There may be several of various sizes in one neuron They are most frequent in the cytoplasm between the nucleus and the dendritic prolongations of the neuron They often occur in the first part of the dendride and in such instances are elongated The characteristic inclusion body contains an inner structure of basophilic staining granules These granules vary from 0 2 to 0 5 micra in diameter and are surrounded by a clear zone in most stained preparations The larger inclusions have a central granule and one or more layers of these inner bodies separated by a finely granular ground substance or matrix Though the matrix is basically eosinophilic as to staining reaction it tends to take on a composite stain bluish pink in preparations stained with eosin methylene blue and mauve in carbolfuchsin methylene blue preparations Small inclusion bodies are more abundant than the larger forms and these are less characteristic in appearance Some contain a central blue granule but most of them are uniformly acidophilic

The characteristic inclusion bodies are more typical and abundant in the Ammon s horn of the hippocampus than in any other part of the central nervous system In this area they are especially numerous in the large neurons about the granule cell layer Typical inclusion bodies generally are demonstrable in the pyramidal cells of the cortex the Purkinje s cells of the cerebellum and the larger neurons of the basal ganglia and cranial nerve nuclei The scarcity of typical inclusion bodies in the pons and medulla is probably explained by the rapid destruction of the neurons When the disease has been of short duration inclusion bodies are either absent or predominantly small with only occasional large forms When the disease has been of long duration inclusion bodies are more numerous less scattered in distribution and there are relatively more large forms The neurons of the ganglionic layer of the retina may contain inclusion bodies

When Negri discovered the inclusion bodies of rabies he believed they represented a form in the development of a protozoan like parasite Subsequent studies of the inclusion bodies of rabies as well as of other diseases indicate that although they may contain the elementary bodies of the virus their structure is made up largely of a matrix derived from the cell protoplasm The matrix of the inclusion body of rabies appears to be largely composed of saturated fatty acids and sterols as shown by

their staining reaction There does not seem to be any definite relation between the occurrence of inclusion bodies and the concentration of virus as determined by titration in animals

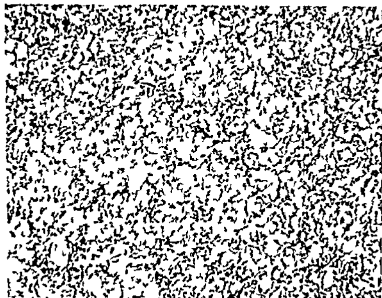
The studies of Goodpasture suggest that the inclusion bodies may be derived in part from the neurofibrillar and mitochondrial apparatus The occurrence of small eosinophilic and basophilic granules in the cytoplasm of degenerating neurons is noted often There is no satisfactory evidence to indicate that these represent the elementary bodies of the virus

Ganglia — Before the discovery of the specific inclusion bodies of rabies the examination of histological sections from the superior cervical sympathetic ganglia formed the principal method for the microscopical diagnosis of rabies The nerve cells here show acute degeneration and are surrounded by large mononuclear cells in a rosette like arrangement (Fig 4) It is believed that the Schwann sheath cells hypertrophy to form the first layer of large cuboidal cells which have a distinctive appearance The interstitial tissue of the ganglia often is heavily infiltrated by mononuclear cells The neurons show degenerative changes similar to those described in the brain Vacuolization of the cytoplasm is however more pronounced in the neurons of the ganglia

The superior cervical sympathetic and gasserian ganglia present the most characteristic lesion but the same changes occur to a variable degree in the other sympathetic and dorsal root ganglia Similar pathological changes have been reported in diseases other than rabies Furthermore the lesion is not likely to be very definite where the disease has been of short duration

Nerves — The nerves supplying the region of exposure in human cases of rabies rarely have been studied Dogs experimentally infected with rabies by inoculation of street virus into a peripheral nerve serve to illustrate the pathology of affected nerves Sections central to the point of inoculation show coalescence of the neurofibrillae and fragmentation of axis cylinders vacuolization of the myelin sheath and a variable degree of chronic inflammatory reaction in the lymphatics of the nerve sheath

Other Organs — The mucosa of the conjunctiva and upper respiratory tract often exhibits an acute inflammatory reaction The mucous glands of the submucosa may show acute degeneration of the acinar cells The salivary and lacrimal glands may be normal in appearance In some cases there is marked acute degeneration of the acinar cells especially those of the mucous type and the interstitial tissue is infiltrated by mononuclear cells (Fig 5) Glands so affected generally contain a high concentration of virus Although various types of granules and vacuoles are apparent there is no satisfactory evidence that specific inclusion bodies are formed



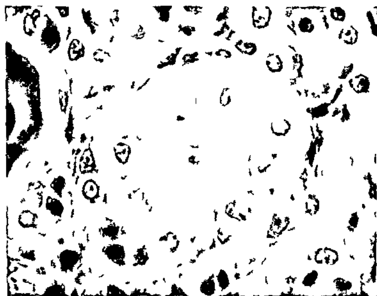


FIG 4 (top) Taraffin section f the ubmaxillary gland of a dog experimentally nfected ith ral es glan l positive f r iru modified eo inmethylene blue tain magnificati n 100 photograph by J B Haulenb ck

FIG 5 Parafhn ectic n of tl up rior cerv cal ympathetic gangl on of a dog expr mentally infected with rabie llu trat ng the neur nal degenerati n m lified eosinmethylene blue ta n magn fication 1 000 photograph by J B Haulenbeck

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The ducts are normal but *may be markedly distended with inspissated* material which appears to be largely made up of mucus The medullary cells of the adrenal gland often show acute degeneration associated with mononuclear cell infiltration of the medulla The adrenal cortex is not appreciably altered in appearance The tubule cells of the kidney may show acute degeneration but inflammatory cellular infiltration of the interstitial tissue is seen rarely The gastrointestinal tract shows no significant alteration other than congestion and edema of the mucosa The neurons of the sympathetic plexuses may show changes similar to those described in the ganglia The other abdominal organs show no characteristic pathology

The secreting cells of the sweat glands of the axilla may show acute degeneration The acinar cells of the breast tissue may exhibit a similar change The eyes are not remarkable except for degeneration of the neurons of the ganglionic layer of the retina The internal ear apparently is not affected except for neuronal degeneration

The pathological changes in the central nervous system of persons dying of rabies are similar to those found in some other diseases notably typhus fever poliomyelitis and rabies treatment paralysis When specific inclusion bodies are not demonstrable sometimes it is impossible to make a pathological diagnosis of rabies The diagnosis then depends on animal inoculation and isolation of the infecting agent

Laboratory Diagnosis of Rabies

Microscopical Examination of Animal Brains

For microscopical diagnosis it is necessary to use a procedure that can be completed quickly and one which produces uniform results It has been found that the inclusion bodies of rabies when present are readily demonstrated in smears or impressions of the Ammon s horn of the brain stained by the method of Sellers (Fig 2) This staining procedure is most practical because the preparation is fixed and stained at the same time and the preparation of the stain is simple and inexpensive The impression method is good because there is little distortion and rupture of cells however some prefer the smear method because more tissue will be obtained on one preparation

To make an impression preparation it is best to cut a 1 to 2 mm cross section from the middle of the Ammon s horn and place this on a piece of blotting paper Using a clean glass slide several impressions are obtained by pressing the slide down on the cut surface of the section

stain readily demonstrates the inclusion bodies However unless the worker is experienced in the use of this method the results are not likely to be uniform Hematoxylin and eosin with formalin fixed tissue occasionally gives fairly good results but this more often is entirely unsatisfactory The water soluble eosin yellow stain if used according to the method of Mallory and where the pH of the stain is not adjusted to the acid side is likely to give similar results

When the microscopical preparations are from human material there is little chance of making a mistake by confusing the inclusion bodies of rabies with those which occur in other diseases In dog brains however inclusion bodies sometimes are encountered which though similar to those occurring in rabies are caused by other conditions notably canine distemper A trained observer will recognize these inclusions as they are pale red and more refractile than those due to rabies and have no inner structure They also tend to irregularity in outline and occur more frequently in the thalamus and lentiform nuclei than in the Ammon s horn

Atypical intracytoplasmic inclusion bodies may be found in the brains of mice which do not have rabies These in all probability are due to a natural virus disease of mice These inclusions are pink to bright red in color very refractile uniformly round and do not have any inner structure They show usually a blue staining margin

Animal Inoculation

It is a well known fact that Negri bodies cannot be found always in men and animals dying of rabies Therefore if the microscopical examination of a brain specimen is negative it is necessary to resort to animal inoculation in order to establish the diagnosis In the past the guinea pig and rabbit have been considered the most suitable test animals for this purpose Since the demonstration that the intracerebral injection of rabies virus into white mice produces a typical and constant infection the white mouse has become increasingly popular as a test animal The chief advantages of the mouse as the test animal are the low cost making it possible to use several animals for one specimen the relatively short incubation period 6 to 10 days for street virus and the consistency of production of inclusion bodies in mice inoculated intracerebrally with street virus

A positive microscopical diagnosis is sufficient proof for the diagnosis of rabies When the microscopical examination proves negative or questionable a pool of the medulla basal ganglia and cerebral cortex should

While still wet layer over with Sellers stain for about ten seconds rinse under the tap blot and dry The preparation then is ready for examination The impression may be covered with a cover slip mounted in balsam or examined directly under oil

Sellers' Stain

Stock Solution

a) Saturated solution of basic fuchsin in methyl alcohol
b) Saturated solution of methylene blue in methyl alcohol

Staining Solution

Stock basic fuchsin	3 5 c c
Stock methylene blue	15 0 c c
Methyl alcohol	25 0 c c

The staining solution can be kept in a dropper bottle and if stored in a refrigerator when not in use it will be good for several months

The inclusion bodies of rabies when stained by Sellers method appear mauve to pink red in color and the basophilic staining inner bodies are well demonstrated The cell cytoplasm nuclei and nucleoli stain blue and the interstitial tissue and fibrillae stain pink (Fig 2)

There are a variety of staining procedures that may be used for impression and smear preparations Most of these require special fixation prior to staining Fixation in methyl alcohol with or without picric acid generally is used for smears and impressions For paraffin work acetic Zenker s solution seems to be the best fixative The preparations then may be stained with Mallory s or Mann s eosin methylene blue or Giemsa s or van Gieson s stains There are a variety of modifications of these procedures

If the eosin methylene blue technique is employed the most satisfactory results are obtained when the alcohol soluble ethyl eosin is used (Fig 3) This is made up in a concentration of 1 per cent in 95 per cent ethyl alcohol This solution should be adjusted to a pH of 3 5 to 4 5 with acetic acid as recommended by Stovall The slides should be kept in this stain for about 30 minutes The methylene blue counter stain should be alkaline and the method of Unna is preferable Five minutes is sufficient time for the counter stain The sections then are differentiated in absolute alcohol containing a small amount of rosin This technique is applicable also to smear and impression preparations Goodpasture s method with carbolfuchsin methylene blue is excellent for demonstrating the inclusion bodies but the nucleoli tend to take the red stain, which may be confusing Wolbach s modification of Giemsa s

The presence or absence of inclusion bodies in rabid animals depends to a considerable extent on the duration of the disease before the animal is killed or dies of rabies For that reason it is advisable to hold biting dogs in quarantine rather than to kill them immediately and send the brain to a laboratory for diagnosis There is a double reason for this First it will allow observation for symptoms of rabies in the animal and as the mortality is to all intents 100 per cent if the animal has rabies it will die Secondly the longer the animal is allowed to live the better the chance of obtaining a positive microscopical diagnosis This is substantiated by the author s observations of experimentally infected dogs Of 188 dogs infected with rabies by intramuscular inoculation of street virus and allowed to die 87 per cent of the animals that lived over 3 days were positive for inclusion bodies Only 48 per cent of the dogs developing paralytic rabies were positive by microscopic examination

Biting dogs i e those with furious rabies are apt to live three or more days after the onset of symptoms and a positive microscopical diagnosis probably can be made in about 90 per cent of animals so affected

Prevention of Rabies after Exposure

Local Treatment

It is imperative that lacerations abrasions or scratches occurring as a result of exposure to rabid animals be given prompt local treatment The experimental work of Galtier Remlinger and Rosenau and the author s own observations have shown that infection can be produced readily in animals by rubbing the virus into the scarified skin Wounds in areas heavily supplied with sensory organs such as the face and hands are especially dangerous Wounds penetrating the muscle tissue probably are even more serious

The experimental work of Follen Cabot and Rosenau form the basis for the use of nitric acid for the treatment of dog bite wounds to prevent rabies They showed that cauterizing with nitric acid was highly effective in preventing the disease in guinea pigs exposed by intramuscular injection of rabies virus even when performed twenty four hours after inoculation Partial protection was obtained in those treated forty eight hours after inoculation More recently Shaughnessy and Zichis have compared the effectiveness of nitric acid 20 per cent green soap solution and tincture of iodine for the treatment of wounds in experimentally infected guinea pigs They found that the green soap solution was as effective as nitric acid where the treatment was carried out within two hours after exposure Tincture of iodine was less effective

be ground in a mortar using some abrasive such as sterile sand or alundum and diluted with distilled water to make a 10 per cent suspension This is centrifuged and the supernatant fluid saved for animal inoculation For diagnostic mouse inoculation 0 03 c c should be injected intracerebrally into each of 4 to 6 mice using a ½ inch 27 gauge needle and a ¼ c c tuberculin syringe No antiseptic is necessary over the surface of the head as bacterial infection of the brain rarely develops unless the material used for injection is contaminated When bacteria are seen in the microscopical preparation small portions of the brain should be placed in pure glycerin for a period of one week or if it is necessary to avoid delay, the supernatant fluid from the brain suspension may be treated with 0 5 per cent phenol for 6 hours which rarely destroys enough virus to alter the results Treatment with 1 5 000 merthiolate solution may be used also

Any of the various strains of white mice are equally suitable as test animals The injected mice should be held for 30 days When 4 mice are inoculated with each specimen except in rare instances one or more will develop rabies by the seventh to eighth day if the specimen is positive Mice developing symptoms are to be killed and impression preparations made from a cross section of the brain through the Ammon s horn area are to be stained with Sellers stain This is necessary as other virus diseases may produce symptoms similar to rabies The inclusion bodies of rabies usually are demonstrable in mice 2 days before the development of symptoms following intracerebral inoculation with street virus

In the series of human rabies case records collected by the author 42 had reports of the microscopical examination of the brain Of these 12 or 29 per cent were negative for inclusion bodies The demonstration of inclusion bodies in the brains of rabid animals who have bitten human beings is of importance in order to determine whether the person bitten was really exposed to rabies In 1913 Negri and Luzzani reported the results of a study of 4 961 brain specimens by both microscopical examination and animal inoculation No inclusion bodies were demonstrable in 6 7 per cent of the specimens proved positive for rabies by animal inoculation J Koch and G Jahn published a similar survey of the specimens received at the Robert Koch Institute at Berlin from 1913 to 1929 A total of 4 682 specimens were found positive for rabies by animal inoculation and of these 11 8 per cent were negative for inclusion bodies In a series of routine brain specimens obtained from the Georgia State Health Department during 1937 771 were positive for rabies by mouse inoculation Of these 81 or 10 5 per cent were negative for inclusion bodies

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The first and most important step in treating wounds produced by rabid or suspected rabid animals is thorough cleansing with warm water and soap In this way the saliva can be removed and bleeding en couraged before cautery is applied Cleansing of deep lacerations can be carried out effectively with a syringe For the present in the opinion of the author all patients should receive local treatment with nitric acid Because of its diffusibility and penetration it remains the surest method of destroying the virus in puncture wounds and especially of penetrating the tissue and killing the virus if local treatment is delayed The wound should be sponged dry and the nitric acid applied with a capillary pipette or wooden applicator Especial care should be taken not to miss small superficial abrasions and the margins of the torn skin of larger wounds should receive particular attention Where the wounds are severe the cauterization should be performed under anesthesia Following cauteri zation with nitric acid the wounds should be treated with a solution of sodium bicarbonate

There are occasions where children are so badly lacerated about the face that thorough cauterization with nitric acid is not feasible In such instances the author recommends thorough cleansing of the wounds with green soap solution followed by nitric acid cauterization of superficial abrasions puncture wounds and the margins of the lacerated skin

As has been noted previously there are records of large series of cases of exposure to rabid animal bite treated only by incision and actual cautery or other local treatment with a very low mortality rate In view of this too much reliance should not be placed on the post-exposure vaccine treatment

Vaccine Treatment

Rabies vaccine of one type or another is recommended by public health authorities throughout the world for the treatment of exposed per sons The remarkably low mortality in treated persons has been con sidered adequate proof for its use despite the absence of satisfactory data as to the susceptibility of man to rabies and the effect of local treatment alone

There are a variety of vaccines available for the treatment of persons exposed to rabies There is no clear cut evidence that any one is superior in preventing the disease

Treatment Failure Rate — McKendrick has presented several analytical reviews of the reports of Pasteur Institutes on human rabies vaccination In his eighth review he included 705 855 completed treatments with

2 676 treatment failures a mortality rate of 0 38 per cent It must be noted that the Pasteur Institutes do not consider as treatment failures those cases that develop symptoms within two weeks after the completion of treatment There were 5 943 persons bitten on the face and the treatment failure rate for this group was 1 83 per cent Kraus Gerlach and Schweinburg analyzed 3 646 case records of persons bitten on the head and given the vaccine treatment A total of 211 of these died of rabies or 5 51 per cent Discarding those cases which occurred prior to two weeks after completion of treatment they listed a reduced treatment failure rate of 1 89 per cent

Despite the marked differences in the preparation of various human rabies vaccines there does not seem to be any significant statistical difference in the results obtained by the various methods

Criteria for Treatment —Several factors are to be considered before advising rabies vaccine treatment for persons bitten or scratched by dogs cats or other domestic and wild animals First it should be ascertained whether there has been any rabies reported in areas where the patient had resided during the previous year next whether the animal was apprehended or killed If the animal was captured it should be turned over to a veterinarian and he should be consulted as to whether there are any clinical signs of rabies If the animal is clinically normal it should be quarantined for 14 days The attending physician should be notified immediately if the animal subsequently shows clinical signs of rabies If the animal was killed or dies while in quarantine the brain should be submitted to a diagnostic laboratory for microscopical examination When the laboratory is located at some distance the animal head should be dispatched in a water tight container packed in ice Unfortunately persons are often bitten by a stray dog which is not apprehended or which has been killed immediately In such cases an attempt should be made to ascertain the behavior of the animal before the person was bitten and an attempt should be made to locate the animal if it ran away Taking these factors into consideration the following procedure is recommended Rabies vaccine treatment is to be started immediately when a person has been bitten or scratched under the following conditions

1 The animal was apprehended and presented clinical signs of rabies
2 The animal was killed and the brain found positive for rabies by microscopical examination
3 The animal was killed and although the brain was negative the animal was suspected of being rabid
4 The person was exposed by a stray animal which escaped and where rabies was known to be present in the community

The vaccine treatment is recommended also for persons who have handled animals diagnosed as rabid by clinical or laboratory means and when fresh abrasions of the skin were contaminated by the saliva of the infected animal

It must be emphasized that when an animal is apprehended after attacking a person and rabies is suspected it should not be killed but should be confined under supervision of a veterinarian If the animal has rabies usually it will die within 2 to 3 days This is important as the immediate laboratory diagnosis of rabies depends on the demonstration of specific inclusion bodies in the brain of the animal and these often are absent in the early stages of the disease

It is apparent then that treatment should be begun if the biting animal though apparently normal at the time of biting later develops clinical signs of rabies while in quarantine Treatment may be discontinued if the biting dog held in quarantine remains well for 10 days

The mouse inoculation test for the diagnosis of rabies in animals has a limited value as regards the question of rabies vaccine treatment. However when an animal is killed immediately after biting a person and the brain is examined and found negative by microscopical examination a confirmatory mouse inoculation test should be performed If the test is negative it reassures the patient who might otherwise live in fear of developing the disease

Vaccines Containing No Live Virus

Semple Vaccine —A number of state health departments in this country prepare and dispense this vaccine free of charge It is also available commercially The vaccine is prepared from the brains of rabbits killed when prostrate with fixed virus rabies An 8 per cent suspension of finely ground brain material is made up in normal saline containing one per cent phenol This is incubated for 24 hours at 37° C It is then diluted with an equal volume of normal saline to make a 4 per cent brain emulsion in normal saline containing 0 5 per cent phenol The vaccine then is stored in a refrigerator The dose is 2 c c and the usual scheme consists of 14 daily subcutaneous injections

Cumming Vaccine —This vaccine is used by the Michigan State Health Department It is also available commercially There have been some modifications of Cumming s original method but in general they are similar in that a 1 or 2 per cent suspension of rabbit brain fixed virus in distilled water is treated with 0 1 or 0 2 per cent formaldehyde solution The formaldehyde then is dialyzed out through collodion tubes immersed

in running distilled water A small amount of tricresol then is added as a preservative The vaccine is dispensed in 2 c c amounts which constitutes the final dosage Fourteen to 21 daily doses are recommended

Kelser Vaccine — This is available commercially but as yet has had only a limited clinical trial The virus is completely inactivated by exposure to one per cent chloroform at refrigerator temperature The human vaccine contains 25 per cent brain and cord tissue in normal saline The treatment consists of 14 daily injections of 0 5 c c vaccine

Live Virus Vaccines

Pasteur Vaccine — The dried cord vaccine is no longer recommended by health officials in the United States and is not available on a commercial basis A number of Pasteur Institutes in other countries still use this method The treatment usually is begun with a five day cord and ended with a one day cord The dosage is 2 c c of a 5 per cent tissue suspension in normal saline The treatment takes 14 to 21 days depending on the severity of exposure

Sellers Vaccine — This vaccine is prepared and dispensed by the Georgia State Health Department It is not available commercially The treatment recommended depends on the severity of the exposure The usual treatment consists of 21 daily injections of 2 c c of a 1 150 suspension of rabbit brain fixed virus made up in 20 per cent glycerin saline containing 0 5 per cent phenol For severe exposures three injections are given daily increasing the concentration of the brain suspension to 1 100 on the seventh day and 1 50 on the tenth day and finishing the course in 15 days

Harris Vaccine — Harris introduced the use of desiccated virus for human vaccine treatment The dosage is calculated by the titre of the dried virus In the original method the treatment was begun with 500 M L D virus followed by increasing concentrations of virus until the fifth sixth or seventh days when 3 000 M L D were administered A modified Harris vaccine is now dispensed commercially The dosage is the same for each day Each dose consists of a calculated dosage of rehydrated virus and 14 daily injections are recommended

Reactions to Rabies Vaccine Treatment

The administration of repeated injections of human rabies vaccine may be followed by a variety of local and general reactions This is to

be expected in view of the amount of foreign protein introduced and the number of injections that are required Since the introduction of this treatment a number of reasons have been advanced to explain the neuritic and paralytic manifestations that sometimes occur At first these reactions were attributed to the presence of live virus in the vaccine, but in view of the occurrence of such symptoms following the administration of vaccines containing no demonstrable virus the present opinion seems to be that the reactions are on an allergic basis that is sensitization to the brain tissue in the vaccine

The studies of Schwentker and Rivers support the theory that these reactions are due to sensitization to the brain protein They found that brain tissue could function as a complete antigen which was organ specific rather than species specific

Acute General Reaction — This occurs in persons who have been sensitized previously to rabbit brain protein It is characterized by syncope or general urticaria or angioneurotic edema This is an infrequent complication and is relieved quickly by adrenalin

Delayed Local Reaction — This is characterized by erythema and edema about the site of vaccination with accompanying pruritus pain and tenderness The wheal like skin lesion may be 3 to 5 cm in diameter There may be slight malaise and a slight rise in the body temperature This reaction is most likely to develop on the seventh to eighth day of treatment and tends to subside despite continued treatment A second flare up may occur again on the fifteenth to sixteenth day of treatment when 21 injections are being given This type of reaction is quite frequent and should cause no alarm

Severe Delayed Reaction — Here the delayed local reaction symptoms are accompanied by constitutional symptoms such as headache, fever, nausea lymphadenopathy and general malaise This type of reaction should warrant careful consideration before continuing treatment, as neuritic and paralytic manifestations are prone to develop if the treatment is continued An acute encephalitis may develop also The severe delayed type of reaction is relatively uncommon It is not apt to begin until after the seventh or eighth injection

Peripheral Neuritis — This develops most often during the latter part of the treatment course and may be accompanied by fever The symptoms often are referable to the facial nerve Neuritic symptoms involving the spine and lower extremities are next in frequency

Dorsal Lumbar Myelitis — This is characterized by fever and gradual onset of weakness numbness and tingling of the lower extremities Patients thus affected usually recover Treatment should be discontinued

if not already completed This complication may occur at any time from the tenth injection to one week after completion of treatment

Paralysis of Landry s Type —This symptom complex usually is ushered in by high fever headache nausea vomiting girdle pains urinary retention and ascending paralysis of the lower extremities It may come on after 5 to 10 injections or any time up to two weeks after the com pletion of treatment The paralysis may progress to involve the bulbar nuclei resulting in respiratory and cardiac arrest Recovery may be rapid or gradual over a period of months In rare instances there is permanent disability The mortality rate appears to be about 30 per cent

McKendrick in his eighth analytical review of reports from Pasteur Institutes on the results of antirabic treatment listed 112 paralytic accidents with 38 deaths from a series of 703 980 treatments From re ports of rabies treatment reactions in the United States it appears that about one in 3 000 persons treated will develop treatment paralysis Treatment reactions are more common in persons who have had previous courses of treatment

Author s Recommendations for Treatment with Vaccine

The author recommends the Semple vaccine for treatment of persons exposed to rabies Fourteen daily injections of 2 c c of this vaccine are to be given beginning as soon as possible after exposure The scheme of treatment for children is the same as that for adults The vaccine should be given subcutaneously in the abdominal area using a different site for each injection It should be made certain that the needle is not introduced into a vein Adrenalin should always be at hand to treat an acute reaction if that appears There is no evidence to support the use of a more intensive scheme of treatment for persons severely bitten During the course of treatment the patient should be permitted to lead a normal life

The occurrence of local reaction to the injection of vaccine does not contraindicate the continuation of the treatment but the development of general symptoms either acute or delayed especially neurological mani festations warrant prompt discontinuation of the treatment

It must be noted that as a rule the patients exhibit no discomfort of any kind from the treatment and severe reactions are rarely encountered Patients receiving a second course of treatment should be watched carefully as most of the severe reactions occur in such cases

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was responsible for the dog control program The Livestock Sanitary Association acting under the Federal Bureau of Animal Industry is the best agency for carrying out such legislation in this country To date the authorities have been handicapped by the failure to include the dog under livestock acts and regulations In order to obviate antipathy on the part of the public to collecting dogs and to the enforcement of regulations on owned dogs the local enforcement of the regulations should be in the hands of a competent veterinarian acting in accord with the State Health Department and the State Veterinarian Rabies in animals should be a reportable disease and these reports should be available to both the State Health Officer and State Veterinarian

In districts where rabies is present in the dog population certain regulations are imperative When a rabid dog is found every effort should be made to locate the owner and find out where the dog has been seen and what animals were exposed All animals bitten by the dog should be killed The potential long incubation period and possible carrier state make this important Where valuable animals have been exposed they may be allowed to live *if kept in quarantine for six months* A quarantine for all dogs in the immediate territory should be imposed at once and kept in force until 90 days after the last reported case of rabies All owned dogs are to be kept on the owner s premises or on leash and any *dogs running free should be impounded The authority in charge of dog* control regulations should notify transportation companies regarding the quarantine and also the inspectors in adjoining districts No dog should be allowed to leave an area which is under quarantine

The use of vaccination of dogs as a means of controlling rabies was not considered practical until Umeno and Doi in 1921 introduced a single injection method of immunization They stated that one injection of a 25 per cent phenolized fixed virus brain emulsion containing live virus would produce immunity to rabies Vaccination of dogs subsequently was made compulsory in Japan The sharp decline in the incidence of rabies for that country cannot be entirely attributed to vaccination as other dog control regulations were enforced also Eichhorn and Lyon in 1922 introduced the Umeno and Doi vaccine in the United States and this method was used on a considerable scale until the U S Department of Agriculture passed a ruling that canine rabies vaccine must not contain live virus This law was passed because occasional vaccinated dogs developed fixed virus rabies Reichel and Schneider in 1923 and Schlingman in 1925 reported that a single injection of phenolized vaccine containing no live virus was effective for immunization of dogs Their work was not substantiated by Schoening in 1930 Barnes Metcalf Martindale and

Control of Rabies

Due to the lack of concerted action in establishing rigid dog control legislation rabies has continued to be prevalent in the United States Vectors other than the dog have played but a minor part in the propagation of the disease in this country Where rabies has become established in wild life species it has been possible to control the disease by reduction of the species of wild life affected

The best example of the effect of rigid dog control regulations on the incidence of rabies is the program which made possible the eradication of the disease from England The procedures used were similar to those carried out in Sweden Norway Denmark Prussia and Switzerland The following sanitary procedures were enforced

1 Imposition of a tax on all dogs
2 Seizure and destruction of all ownerless and wandering dogs
3 Destruction of all dogs with rabies or suspected of being or becoming rabid
4 Requirement that all other dogs wear a properly constructed and well fitting muzzle while rabies prevails and for a period of the longest latency after the last reported case
5 Subjection of all imported dogs to a six months quarantine period

Taxation is a necessary factor in dog control legislation It allows collection of data as to the number of dogs in a given area and shows the ownership of a dog by the attached license It also secures some reduction in the total number of dogs The ownership of dogs then is largely limited to those who will take good care of the animals and who assume responsibility for the same It is generally agreed that unspayed female dogs should be subject to a higher tax than males and spayed animals This is essential because it will lessen the number of mongrel dogs that so often become strays Then too the female dog in heat attracts large groups of dogs which in fighting may cause the infection of numerous animals should one be a carrier or in the early stages of the disease

The ownerless and wandering dog is a menace where rabies is prevalent All are agreed that these animals should be eliminated but in order to do this funds and a suitable personnel must be available to collect such animals This control measure then to a certain degree rests on taxation of dogs as this makes the funds available to carry out such a program

The question then arises Who is to have the responsibility of enforcing dog control legislation? In England the Department of Agriculture

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Lentz in 1934 or Webster in 1939 Kelser introduced a chloroform inactivated canine rabies vaccine in 1930 Although experimental studies have produced some evidence that this as well as other types of vaccines containing no active virus will produce immunity in the dog the lack of properly controlled experiments have led to conflicting reports as to the value of vaccination in controlling rabies

It is difficult to determine the value of vaccination from the reports of its use in the field control of rabies Other sanitary measures usually are included Johnson and Leach have shown that one 5 c c subcutaneous injection of canine rabies vaccine containing no demonstrable live virus can produce a high resistance in the dog to intramuscular inoculation of street virus In one test 50 dogs were given a single 5 c.c dose of chloroform inactivated canine rabies vaccine containing $33\frac{1}{3}$ per cent brain material and tested one month later by injection of street virus into the masseter muscles Only 2 of these dogs died of rabies 4 per cent compared to 34 of 55 control dogs similarly inoculated 62 per cent A test of a phenol inactivated vaccine of the same brain concentration produced a similar degree of protection Four states in this country have adopted compulsory vaccination, but the law has been difficult to enforce and although a reduction in the incidence of rabies has been attained the disease has continued to occur

Vaccination of dogs no doubt can be a useful adjunct to the dog control regulations previously mentioned and might be made compulsory in infected areas but vaccinated dogs should not be allowed special privileges

When rabies becomes established in wild animals it is necessary to institute a vigorous trapping and hunting program to reduce drastically the number of animals When rabies is found to be present in a wild animal species the state and federal wild life agencies should be notified immediately and they will supervise the control program Vampire bat rabies apparently has been eradicated from Trinidad in British West Indies by a drastic reduction of the bat population A similar program is under way in South American countries where the vampire bats are known to be infected Large scale vaccination of domestic animals with phenolized live virus rabies vaccine has been used in Brazil and Venezuela with apparent success

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CHAPTER XXVII

SPRUE

By FREDERIC M HAYES

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Synonyms — Psilosis Indische spruw Cochin China diarrhea chronic endemic enteritis of hot countries intestinal moniliasis idiopathic steatorrhea celiac disease Gee Herter disease

Definition — Sprue is a chronic deficiency state with a marked tendency to remissions and relapses characterized when fully developed by glossitis and stomatitis anorexia gastrointestinal indigestion by the passage of large fatty frothy foul smelling stools by great loss of weight generalized muscular wasting and in adults and some children by macrocytic hyperchromic anemia

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climates This was pointed out by Edward Jenner Wood[1] many years ago and Thaysen[7,9] recently has emphasized the fact More than a hundred cases of so-called non tropical sprue are on record[11] and it is certain that many more have gone unrecorded and still more undiagnosed Wider familiarity with the syndrome should lead to its more frequent recognition Inadequacy of the food intake and not latitude is the determining factor in the production of the sprue syndrome

Etiology

All observers are agreed that dietary deficiencies play a large part in the causation of sprue and until recently it was treated almost entirely by special diets Modern researches have defined more clearly the nature of the under lying deficiency but the exact etiology of sprue still is unknown It may how ever be safely asserted from the accumulated evidence that the sprue state is due in last analysis to functional impairment of the gastrointestinal tract Sprue and pernicious anemia are closely related deficiency states and the light which the work of Minot and Murphy Castle Cohn Sturgis and Isaacs and others[12] have shed on the etiology of pernicious anemia has aided greatly in clarifying the etiology of sprue During the normal process of protein digestion certain highly essential but as yet unidentified substances are produced which are ab sorbed by the intestinal mucosa and stored chiefly in the liver In both sprue and pernicious anemia there is a defect in this mechanism but whereas in pernicious anemia the gastric secretion has lost the power of forming these essential sub stances in sprue the error usually but not always is one of deficient absorption rather than of defective production

The deficiency in sprue possibly may arise in four ways (1) by a dietary deficiency of the extrinsic factor to use the terminology of Castle (2) by a defect of gastric digestion due to lack of the intrinsic factor (3) by poor ab sorption from the intestine and (4) by deficient storage by the liver [3,14] A com bination of several of these defects may exist

The primary defect in the sprue syndrome is one of intestinal absorption As a consequence although in the sprue patient fats are normally split since the pancreatic secretion is maintained they are so poorly absorbed that they are ex creted in two or three times the normal amount Calcium and phosphorus are as a rule not well absorbed leading often to low serum values for both with tetany osteoporosis dwarfism and rickets as not infrequent consequences Sug ars apparently are not well absorbed but proteins are so well assimilated that there is no marked azotorrhea such as is found in pancreatic deficiency[9]

The important work of Miller and Rhoads [5] sheds a new light on the mode of action of the deficiency which apparently underlies the sprue syndrome By

Historical

Aretaeus of Cappadocia who is said to have practiced in Rome during the second century of the Christian Era has left a description of what he termed cœliac disease which students of the sprue syndrome will recognize as strikingly similar to sprue as observed in modern times[0] The Dutch word, sprouw, signifies an aphthous stomatitis (ulcuscula quibus infantium ora ulcerantur)[1] and was first used by Vincent Ketelaer in 1669 in describing among the Belgians an aphthous stomatitis with feces so copious that ' several basins or pots scarcely hold these accumulations William Hillary an English physician practicing in the Barbados, usually is credited with the first description of sprue which he observed there about 1754 but the clearest modern reports were by Manson[3] in China and van der Burg[4] in Java in the same year, 1880 The disease became known as tropical sprue from the erroneous belief that it occurred only in tropical or sub tropical climates when the same syndrome was found to occur not infrequently in temperate climates, it was called non tropical sprue

Samuel Gee in 1888[5] gave a brief but altogether admirable description of a curious wasting disease seen more often in young children but met with in persons of all ages , which he called ' the cœliac affection " The term cœliac diathesis (ventriculosa passio) is one of great antiquity signifying according to Gee s homely translation ' belly sickness " Herter published in 1908 bacteriological and chemical studies upon a small group of dwarfed children in a bool entitled, ' On Infantilism from Chronic Intestinal Infection Heubner[6] in Germany, unfamiliar with Herter s work, described a condition in young children which he called Verdauungs Insuffizienz or chronic intestinal indigestion It is now universally recognized that Gee Herter and Heubner were describing identical syndromes under different names Thaysen[8,9], as the result of extensive studies was convinced that tropical sprue non tropical sprue and celiac disease are expressions of the same underlying disease state a view with which the writer of this article fully agrees and suggested that the condition be called idiopathic steatorrhea The term sprue, however has priority over all other designations and therefore should be retained

Geographical Distribution

Sprue is endemic in certain countries of the Far East, British India and Ceylon Indo China the Malayan Archipelago, Dutch East Indies Philippine Islands the southern coast of China Korea and Formosa, etc , and in the West Indies For North American physicians however it is of much greater importance to know that sprue occurs not infrequently in temperate and northern

These x ray studies are discussed in detail elsewhere but briefly stated in the sprue syndrome x ray evidences of severe derangement in the muscular contractions of the small intestine usually are demonstrable Hurst writes There are three characteristic and constant features of the syndrome (a) the stools contain excess of split fat but no excess of neutral fat meat fibres or starch and no inflammatory material (b) radiography demonstrates the disappearance of the normal feathery or herring bone aspect of the duodenum and jejunum produced by *the valvulae conniventes (c) no pathological changes are found in the intestine after death* if postmortem damage has not taken place With adequate treatment normal absorption of fat is restored together with the normal radiographic appearance of the small intestine

He suggests that the characteristic feature of the sprue syndrome is the result of paralysis of the muscularis mucosae which would lead to the loss of the pumping action of the villi by means of which fat is conveyed from the lacteal radicles of the villi into the larger lacteals and to flattening of the valvulae conniventes without changes in the normal appearance of the mucous membrane Paralysis of the muscularis mucosae may be secondary to loss of the normal stimulant of Meissner s (submucosal) plexus or to the effect of vitamin deficiency or some toxaemia on the plexus

One serious objection to the theory proposed by Hurst is that the so called deficiency intestinal pattern has been observed in other conditions such as pellagra carcinoma of the head of the pancreas acute gastroenteritis and even in persons who showed no evidence of dietary deficiency nor a steatorrhea Not enough evidence exists for the formation of a final opinion upon the exact significance of intestinal deficiency patterns

That marked impairment of the normal intestinal motility would interfere with absorption cannot be doubted and May and McCreary[17] have published important evidence on this point In a study of forty children suffering from infantile sprue or celiac disease they found quite uniformly x ray evidence of disturbed intestinal motility and low glucose tolerance curves When these patients were treated with acetyl beta methylcholine (mecholyl) a drug which increases tone amplitude of contraction and peristalsis in the gastrointestinal tract the intestinal x ray pattern returned to normal and curves of glucose absorption were elevated in normal fashion indicating increased absorption of sugar

Jones Benedict and Hampton have reported very recently upon direct observational studies of the gastric mucosa in pernicious anemia both before and after liver therapy using the gastroscope and direct observation at operation together with histological studies of biopsied material The evidence obtained convinces them that during relapses atrophy of the gastric mucosa occurs and

feeding a modification of the Goldberger and Wheeler[16] diet No 123, a diet which causes black tongue in dogs a symptom complex was produced in swine, marked by oral mucous membrane lesions, achlorhydria and macrocytic anemia It was impossible to demonstrate any hematopoietic activity of the gastric secretions or livers of such swine when tested on cases of pernicious anemia in man These experiments strongly suggest that a dietary deficiency in man may, in some as yet unexplained way, inhibit the formation of certain products of digestion essen tial to the proper functioning of the blood forming organs and the gastrointestinal tract As Castle Rhoads and associates[14] remark Since the administration of defective diets to animals may produce not only macrocytic anemia but also pro found morphologic and physiologic derangements of the alimentary tract, a cause sufficient to account for the secretory and probably for the absorptive defects of the patient with sprue is exhibited "

Several theories have been advanced to explain the deficient intestinal ab sorption in sprue none of which however, rests upon a secure basis of fact Verzar[13] has sought to explain the deficient absorption of fats and carbohydrates in sprue by the assumption that there exists a defect in the mechanism of phos phorylation which he and others regard as an essential intermediate phase of fat and carbohydrate absorption His contention that the process of phospho rylation is controlled by the adrenal cortex is not convincing and has not been confirmed by others[44]

If it were true that an adrenal cortical hormone controls the absorption of fat steatorrhea should be a constant finding in Addison s disease which is not the case Furthermore, the treatment of sprue patients with adrenal cortical hormones in the Duke Hospital Clinic has been totally ineffective, and others have had a similar experience[3]

The brilliant results obtained, as a rule, in the treatment of sprue by liver extracts has led certain observers to postulate a deficiency of the B complex of vitamins in sprue Suffice it to say that no proof of this theory exists, and the treatment of the sprue syndrome with the B complex or with its separate com ponents has proven quite valueless The enthusiastic claim of Manson Bahr[45] for the curative value of nicotinic acid in sprue is quite lacking in anything re motely resembling scientific proof Nicotinic acid has been used in the treat ment of sprue in the Duke Hospital Clinic without any evidences of favorable therapeutic results Furthermore, in four instances of sprue where the nicotinic acid status was determined, no deficiency of nicotinic acid was found, despite the fact that vitamins C and A were very deficient

Hurst[46] has published recently a mechanical theory to explain the deficient absorption of fats in the sprue syndrome based largely on the work of Verzar and his associates and upon certain x ray observations of American workers[33 35 36]

to a specific infectious causation of sprue, rather are they compatible with the existence of a deficiency state

The Clinical Picture

All of the essential features of the sprue syndrome are traceable to a disordered function of the gastrointestinal tract A careful nutritional history often reveals that the sufferer from sprue has lived on a badly balanced diet, in which carbohydrates and fats have predominated with a quantitative and qualitative deficiency of proteins The syndrome is very prone to occur in patients who are debilitated from some antecedent infection such as amebic or bacillary dysentery malaria or following pregnancy but it may attack others in seemingly good health The onset is insidious as a rule and not characteristic so that its early recognition may be difficult Remissions and relapses are the rule and variability of the clinical phenomena is one of its outstanding features Very exceptionally sprue may run a subacute course *terminating fatally in a year or two* but much more commonly it pursues a chronic course through many years Occasionally especially in children the onset is with a severe acute dysentery

The disease usually begins as a more or less trivial gastrointestinal indigestion with anorexia, flatulence and a feeling of epigastric fulness The patient is ailing and complaining but not very ill The dyspepsia grows worse and malaise anorexia and abdominal discomfort increase The tongue becomes sore and vomiting may occur Eventually copious semi solid or fluid foul smelling stools are passed especially in the early morning There may be one large stool daily, but usually more are passed Within a few months the patient is a chronic dyspeptic abhors breakfast and often begins to limit an already ill balanced diet Meats are thought to be too strong and voluntarily are restricted or eliminated from a diet which then is limited to carbohydrates and fats Unless a diagnosis is made and the dietary deficiency corrected the symptoms grow worse though they often show marked improvement from time to time In the early months the disease yields readily to a proper diet containing abundant proteins and vitamins and even moderately advanced cases may show rapid and astonishing improvement when thus treated This is especially true of celiac disease or the infantile form of sprue (Figs 1 2) Eventually however the evacuations increase from three or four to ten or more in the day and assume a form which is highly characteristic but not pathognomonic of sprue No one has described them more graphically than did Samuel Gee in his original report

Signs of the disease are yielded by the fæces being loose not formed but not watery more bulky than the food taken would seem to account for pale in colour as if devoid of bile yeasty frothy, an appearance probably due to fer

that this atrophic change parallels, and is quite comparable to, the glossitis and papillary atrophy associated with the disease They also observed hypertrophic gastritis in two patients and state that both the atrophic and hypertrophic gastritis disappeared after successful therapy, the mucosa assuming a normal appearance

Twenty sprue patients in the Duke Hospital series were studied gastroscopically by Julian Ruffin, who concluded that there was, apparently, no constant gastroscopic picture in the sprue syndrome However, atrophy of the gastric mucosa was observed in 8, or 40 per cent, of this small number of sprue patients Of 16 patients, who were in an active stage, 9 had normal gastroscopic pictures and 7 showed the picture of atrophy Two patients were examined before and after treatment, both showing marked atrophy at the original examination After satisfactory recovery, one patient showed no change in the gastroscopic picture, whereas in the other the mucosa had returned to normal

It has been suggested by Ashford[17] and others that the disease is due to intestinal infection by *Monilia psilosis* but there is no evidence to support the view that sprue primarily is an infectious disease[14] Secondary infection may accompany the deficiency state, which underlies the disease and be a factor in the production of some of its symptoms, but proof of a specific infection is lacking

The sexes are affected about equally, and no age is exempt Infantile sprue or celiac disease occurs most frequently between the ages of two and five years, often causing dwarfism, whereas adult sprue is more common in middle and later life Members of the white race are far more susceptible than are members of the colored races

PATHOLOGY

The morbid changes found in the gastrointestinal tract at autopsy are surprisingly slight in view of the severe intestinal symptoms of the disease This was noted by Gee[5] and has been confirmed by subsequent observers[7], many of whom have failed to find significant pathological changes in the intestines when the post mortem examination was done promptly after death Now and then evidences of chronic inflammation with small ulcerations in the duodenum and jejunum have been observed probably due to secondary infections The intestines are thin and atrophic, and frequently the large intestine is greatly distended

The fat depots of the body are greatly depleted, and all the parenchymatous organs show marked atrophy Castle Rhoads and associates[14] have shown that the liver of a patient dead of sprue contained no hematopoietic substance The morbid changes found in sprue variable and often slight, do not lend support

side as rapidly as they appear and under proper treatment the tongue within a few days assumes a normal appearance Successive attacks of glossitis lead to atrophy of the filiform papillae while the fungiform papillae remain as red dots on a smooth background eventually the e disappear and the tongue presents a bald, beefy red highly polished appearance (Fig 3)

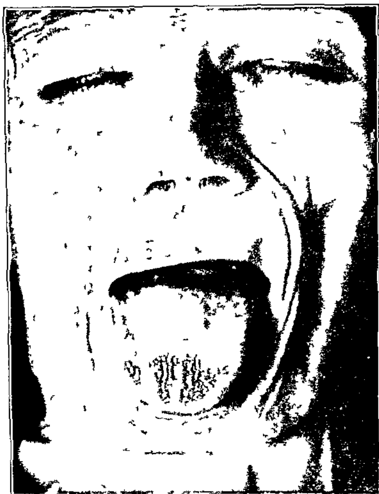


Fig 3 Duke Ho pital No 5 868 Glos itis with papillary atrophy in prue

In a small percentage of prue patients the lesions of the tongue and mouth may antedate the development of gastrointestinal symptoms by months or years

mentation stinking, stench often very great, the food having undergone putrefaction rather than concoction" It should be emphasized strongly that the sprue patient may be constipated or pass only one large stool in the early morning Diarrhea, moreover, is not always complained of, and careful questioning may be needed to elicit a history of disordered bowel movements in the past[15] This is especially true of sprue as seen in temperate climates, where a chronic dyspepsia with sore tongue may be the only gastrointestinal complaint



Fig 1 Duke Hospital No 45653 Infantile sprue (celiac disease) showing the marked emaciation with protuberant abdomen and the querulous facies
Fig 2 The same patient after treatment with a high protein high vitamin diet bananas and liver

As the intestinal features of the disease develop, mouth symptoms and changes in the lingual and buccal mucosa become prominent The tongue assumes a sore 'beefy' and inflamed appearance Hot or highly spiced foods cause intense discomfort Aphthæ may appear in crops of minute whitish vesicles with a fiery red border These burst producing very painful ulcerations 1 to 2 mm in diameter The ulcers rarely are numerous and are evanescent They do not constitute an essential part of the sprue syndrome though probably they occur in all cases at some time during the course of the disease The changes in the lingual mucosa closely resemble those seen in pernicious anemia, they frequently sub

ford remarks, literally dissects its victims It is common for the patient to lose from one third to one half his or her normal weight (Figs 4 5 and 6) This emaciation is one of the most characteristic features of sprue in sharp contrast to pernicious anemia, in which the weight loss is moderate

Anemia gradually develops and the skin assumes a dirty brownish yellow color much like that of a rusty grapefruit Patchy brownish pigmentations of the forehead and malar eminences frequently are seen and may occur symmetrically over the trunk and legs The skin changes are not inflammatory and do not lead to ulceration and desquamation as in pellagra The mucous membranes are not pigmented as is often the case in Addison s disease The liver dulness is markedly decreased There is no fever in uncomplicated cases and the blood pressure is low The basal metabolism is normal or occasionally elevated The urine presents no characteristic changes though it may contain albumin Edema develops occasionally and may be the result of lowered serum proteins Amenorrhea is the rule

The central nervous system shows marked evidence of injury The sprue patient is emotionally unstable often though not always depressed with a strong leaning to pessimism irritable forgetful and filled with vague aches and pains *Insomnia is troublesome Children suffering from infantile sprue are* very difficult nothing pleases them and they are exceedingly irritable and emotional With improvement under treatment the change for the better in the patient s mental condition is rapid and very striking Subacute combined de*generation of the spinal cord does occur * but it is very rare Paresthesia of the* hands and feet is a common complaint

From the foregoing description it will be seen that the sprue syndrome varies considerably both as to symptoms and as to severity It may be well to emphasize *by more extended discussion, some of its distinguishing characteristics*

Blood

In the early stages of sprue there may be a moderate hypochromic anemia while in the fully developed disease in adults the blood picture resembles very closely that of pernicious anemia In celiac disease or infantile sprue the anemia usually is hypochromic though rarely it may assume the hyperchromic macro*cytic type*[19] *The hematopoietic organs of children do not as a rule react to* injuries of any kind by the production of a macrocytic hyperchromic blood picture Pernicious anemia is excessively rare in children With improvement the blood gradually loses its hyperchromic macrocytic character and the color index *falls to normal or below In relapses the blood picture of pernicious anemia again* develops The anemia of sprue however is variable and the findings will de

tongue and mouth sprue, whereas in others there are no symptoms referable to the tongue and mouth and the gastrointestinal symptoms dominate the picture, incomplete sprue Such variations are common in deficiency states

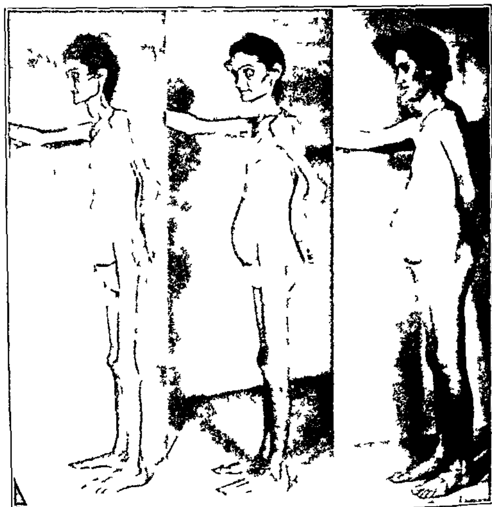


Fig 4 Duke Hospital No 57868 A typical example of a patient suffering from severe prue cachexia

Fig 5 Shows the patient after 30 days of liver therapy

Fig 6 The same patient after 66 days of liver therapy

As the disease becomes chronic, the patient rapidly loses weight with each relapse, though gaining back part and sometimes all of the loss during the early remissions Gradual loss may continue for some years but eventually the weight decreases amazingly and the patient becomes a living skeleton Sprue as Ash

Fat Metabolism Steatorrhea

It is unfortunate that the typical sprue stool as described by Samuel Gee has been accepted as an essential finding in the diagnosis of the sprue syndrome for it frequently happens that the stools in sprue present no characteristic picture Furthermore any of several conditions producing steatorrh a may exhibit stools grossly resembling the typical stools of sprue

All variations in color and consistency are seen from copious fluid evacuations with the appearance of dirty dish water to semi solid or solid and obviously fatty stools Even when the stools of sprue are watery and show but little fecal material quantitative chemical analysis reveals an excess of fat A microscopic *study of the sprue stool both unstained and stained by the use of Sudan III* or nile blue sulphate is useful when positive evidence of fat can thus be demonstrated but frequently such studies do not yield positive evidence of steatorrhea and quantitative fat studies alone will demonstrate the presence of excess fat in the stools

So important are such chemical estimations of total fat in the stools in the diagnosis of sprue that it seems worthwhile to give in detail a method which has proven useful in the Duke Hospital Clinic

Method — Reagents 9N sulfuric acid (approximately) 95 per cent ethyl alcohol ethyl ether U S P petroleum ether U S P

Make stool sample to viscous consistency with distilled water mixing well to homogenize If large particles still remain strain through a No 8 strainer

1 On an analytical balance weigh to milligrams a 5 to 10 gm sample in a tared 50 c c pyrex beaker Dry in oven at approximately 115 C for about 3 hours This will yield dry weight of stool and can be carried on during the fat extraction which is carried out on another sample as follows

2 At the same time weigh out to milligrams a 3 to 5 gm sample of the watery homogenized stool directly into the bottom of a 50 c c round bottom narrow neck centrifuge tube taking care to keep material from sides of tube Add 1 c c of 9N sulfuric acid and make to approximately 5 c c with water Add to this an equal volume of 95 per cent ethyl alcohol Heat in boiling water bath *for 2 minutes Cool thoroughly under running water Add 15 c c of ethyl ether* stopper with cork stopper and shake vigorously Add 15 c c of petroleum ether stopper and shake vigorously Centrifuge at low speed for 5 minutes Transfer the clear supernatant fluid to a shallow bottom 50 c c conical centrifuge tube Evaporate the ether cautiously by heating the tube in a small beaker of hot water taking precautions to prevent bumping For this purpose a small special stirring rod with a curved beaded tip is placed in the tube Repeat the extraction of the alcoholic stool mixture 4 or 5 times using 15 c c portions of ethyl

pend upon the stage of the disease in which the blood is examined In the fully developed untreated disease a hyperchromic macrocytic blood picture is found with great constancy Some observers have attempted to make certain fine distinctions between the blood pictures of sprue and pernicious anemia, but the two diseases cannot be differentiated by blood studies alone the response to liver therapy is identical in both Studies of the bone marrow in sprue reveal changes differing in no way from those found in pernicious anemia The total number of white cells is within normal limits, or low, and the differential leuco cyte count is not characteristic

Gastric Analysis

The demonstration of even small amounts of free HCl after histamine stimu lation is of the greatest value in the differential diagnosis of sprue [31], for this at once separates the sprue syndrome from pernicious anemia Thus, of 56 pa tients in the Duke Hospital series 19 or 35 per cent, showed a total absence of free HCl after hypodermic histamine (0 5 mgm) stimulation In 65 sprue pa tients studied by Castle, Rhoads and associates in Puerto Rico 31 per cent showed achlorhydria after histamine stimulation It is thus seen that from 65 to 70 per cent of sprue patients can be differentiated at once from pernicious anemia by gastric analysis Low HCl values are the rule in sprue, but these tend to rise with clinical improvement and achlorhydria may disappear under treatment, which probably is never the case in pernicious anemia

The occurrence of achlorhydria in apparently normal individuals rarely is sufficiently emphasized [1] Ruffin and Dick[4] in a statistical study of 2 877 gastric analyses done with the use of histamine in the Duke Hospital Clinic found 211 instances of achlorhydria in apparently normal individuals The dis tribution of these by age and sex is shown in Table I

TABLE I

THE OCCURRENCE OF ACHLORHYDRIA IN NORMAL INDIVIDUALS

Age	Total No of Cases		Cases With No Free HCl		% With No Free HCl	
	Male	Female	Male	Female	Male	Female
0– 0	45	36	0	0	0	0
21–30	214	189	10	7	4 5	3 6
31–40	239	230	21	20	8 4	8 0
41–50	179	197	27	29	13 1	12 8
51–60	114	149	32	27	21 9	15 3
61–80	51	63	18	20	6 5	24 1
	842	864	108	103		

tion and from peristaltic anomalies even when the fat has been normally digested Thus gastrocolic and jejunocolic fistulae as well as severe diarrheas may cause steatorrhea[3] The stools of sprue are easily distinguished from those of *pancreatogenous steatorrhea by the fact that in sprue meats are well digested* and absorbed whereas in the fatty stools resulting from deficiency of pancreatic juice undigested muscle fibres are seen microscopically in large numbers, creatorrhea Nitrogen determinations show a marked azotorrhea in pancreatic deficiency but not in sprue The symptom complex of fatty diarrhea azotorrhea and permanent or alimentary glycosuria diabetic in type, presents a characteristic clinical picture of pancreatogenous steatorrhea

Acholic stools do not show the presence of muscle fibres so characteristic of pancreatogenous steatorrhea but the acholia and accompanying jaundice serve to differentiate such stools from the stools of sprue Mesenteric tuberculosis tabes mesenterica may lead to defective fat absorption steatorrhea marked loss of weight, low serum calcium values and osteoporosis However the blood sugar curve after the glucose tolerance test is not low as in sprue the anemia is hypochromic and the finding of tuberculosis elsewhere in the body usually clarifies the diagnosis

The cachexia of malignant disease and infections of the intestine by uncinaria or ameba, which may present superficial resemblances to the sprue syndrome should cause no diagnostic difficulties if the stools are examined carefully It is notorious however that stool examinations often are neglected, and herein lies the chief source of possible errors in diagnosis

Finally it must be emphasized that not all deficiency states fall into classifiable syndromes It is probable that deficiencies are always multiple and the resulting clinical picture will depend upon the preponderant lack of one or more accessory food factors The literature of sprue is sprinkled with reports of such mixed syndromes[9, 18]

Calcium and Phosphorus Metabolism Osteoporosis Tetany Dwarfism Rickets

McCrudden and Fales first noted osteoporosis in celiac disease associated with a negative calcium balance and an inadequate retention of phosphorus Since then osteoporosis frequently has been observed in both infantile and adult sprue[7] Many sprue patients are capable of absorbing adequate amounts of calcium when their food intake is rich in calcium whereas a low calcium diet brings about a negative calcium balance In regions where there is no quantitative or qualitative deficiency of sunlight sprue rarely is attended with low calcium values a fact which may be reasonably explained by the abundance of ultraviolet rays and their power of synthesizing vitamin D from the inactive ergosterol

ether and petroleum ether each time as before, and evaporating the supernatant cautiously after each extraction

The residue from the extractions remaining in the conical centrifuge tube is dried by heating the tube in boiling water bath for 10 minutes, making sure that no alcohol, ether or water remains in the tube Cool and add 30 c c of petroleum ether, washing down stirring rod and sides of tube and stirring up residue well Centrifuge at low speed Transfer the clear supernatant fluid to a tared 50 c c Erlenmeyer flask Evaporate the petroleum ether slowly by heating cautiously on a steam bath Repeat this extraction with 30 c c portions of petroleum ether 4 times transferring the supernatant to the 50 c c Erlenmeyer flask and evaporating off the petroleum ether each time After the last evaporation no petroleum ether should remain

Dry the flask on the outside and place this flask and the beaker from "1", containing the oven dried sample of stool, in a vacuum desiccator for 1 hour Weigh the beaker to milligrams and the flask to tenths of milligrams, using an analytical balance

Calculation

$$\frac{(\text{gm of stool before drying}) \times (\text{gm of fat in flask}) \times (100)}{(\text{gm of dried stool}) \times (\text{gm of stool taken for fat extraction})} = \text{per cent fat}$$

in dried stool

On analysis the fat of the sprue stool has about the following composition fatty acids 55 per cent neutral fat 25 per cent and soaps 20 per cent Thus it is seen that lipolysis occurs in normal fashion, which supports the findings of numerous observers[4] that there is only slight or no deficiency of enzymes in the duodenal fluids The difficulty is one of absorption as demonstrated by the low blood fat curves after the feeding of fats[3, 40] A determination of the total fat in the stool suffices for detailed qualitative analyses are of no value in the differential diagnosis of the steatorrheas

The excess of unabsorbed fatty acids of the sprue stool results in the formation of calcium soaps and an excessive excretion of calcium which produces low serum calcium values This binding of calcium by fatty acids sets free phosphoric acid which is absorbed by the intestine and excreted in the urine, leading to low serum phosphorus values A more extended discussion of calcium and phosphorus metabolism and the clinical evidences of deficiencies of these minerals will be found elsewhere in this chapter

The normal stool contains less than 30 per cent of fatty matter, and any amount in excess of 30 per cent may be regarded as steatorrhea Bile salts and pancreatic juice are essential for the digestion and absorption of fats and consequently when either or both are excluded from the intestine steatorrhea occurs Excess of fat in the stool also results from defective intestinal absorp

of the skin As would be expected the defective calcium metabolism produces its most striking results in infantile and adolescent sprue resulting in dwarfism and rickets with marked deformities of the skeleton

Bennett Hunter and Vaughan have studied 15 patients with the sprue syndrome all of whom showed marked skeletal deformities These individuals varied in age from fifteen to fifty seven years at the time of observation but the age of onset was infancy or early childhood in 10 instances and in the other 5 it varied from ten to fifty two years Ten of the 15 patients were dwarfed and 12 showed osteoporosis spontaneous fractures had occurred in 6 and tetany was present in 14 It is obvious from these interesting and important observations that no sharp separation of celiac disease from adult sprue is possible Celiac disease bear the same relation to adult sprue that cretinism does to myxedema or gigantism to acromegaly Parsons who in 1913 first demonstrated the occurrence of definite rickets in celiac disease has brought forward very complete evidence that the bone changes are rachitic in origin and can be cured or prevented by the administration of vitamin D The dwarfism resulting from infantile sprue (Fig 7) described in Herter s classical monograph may or may not be accompanied by rachitic stigmata When both conditions coexist very bizarre bony deformities are produced and kyphoses and deformities of the long bones may be apparent With low blood calcium values tetany may supervene it is not a rare occurrence in the sprue syndrome

Calcium occurs in the blood in two forms in the diffusible ionized state (Ca^{++}) and as non diffusible calcium which is bound to plasma proteins largely to the albumin fraction Only the ionized calcium is physiologically active the protein bound fraction serving as a reservoir Thus is it seen that for the clinician intere ted as he must be in the objective manifestations of hyper or hypocalcemia knowledge of the amount of physiologically active calcium in the blood is of great importance Until recently no such knowledge could be obtained in any routinely practicable way

McLean and Hastings using the frog heart method for the quantitative determination of ionized calcium have devised an equation which permits of the ready determination of ionized calcium from a knowledge of the total calcium and total protein of the blood serum They have reduced this equation to nomographic form and it seems quite accurate enough for routine clinical work (Chart 1) We have used it routinely on the wards of the Duke Ho pital Clinic and have found it invaluable in the study of hypocalcemic states For example we have observed clinical tetany only three times in our study of 66 sprue patients and in each of these the level of ionized calcium in the serum was at or slightly below the tetany level of 3 mgm per 100 c c of serum We have not observed tetany when the ionized calcium level was above 3 5 mgm per 100 c c

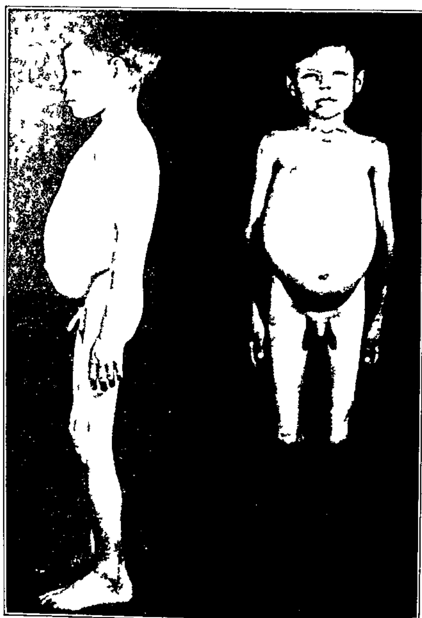


Fig 7 Duke Hospital No 433 Dwarfism in a boy of seventeen as the result of sprue beginning at the age of 18 months

ferentiating the sprue syndrome from pernicious anemia, Addison's disease and pancreatogenous steatorrhea, diseases in which the blood sugar curves are not abnormally low (Chart 2). It is positive in a very high percentage of sprue patients[18]

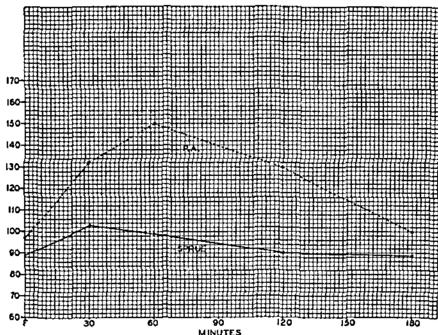


CHART 2 Blood sugar curves in sprue (average of 1 cases) and pernicious anemia (P.A.) (average of 10 cases)

Of 65 sprue patients in the Duke Hospital series only 5 showed a rise in the blood sugar curve after the ingestion of 1.5 grams of glucose per kilo of weight of more than 40 mgm per 100 c c of blood

Protein Metabolism

In sharp contrast to the disturbances of absorption of fats and sugars, so evident in the sprue syndrome the metabolism of proteins seems nearly or quite normal. As judged by the excretion of nitrogen in the feces as compared with the normal there is no significant change. When sufficient protein was fed Thaysen found that the nitrogen balance was positive. In contrast to this the nitrogen content of the stools in pancreatogenous steatorrhea is markedly in

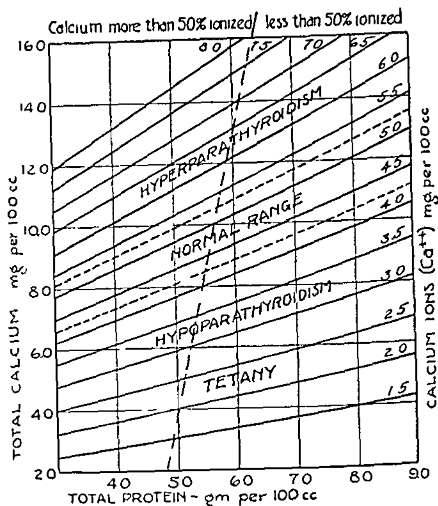


CHART 1 The McLean and Hastings nomogram for calculating ionized calcium from the total calcium and total protein of the serum

Carbohydrate Metabolism Blood Sugar Curves

Low blood sugar curves, following the ingestion of 1 5 gms of glucose per kilo of body weight have been observed in the sprue syndrome by Thaysen and Norgaard[27] and others[9 18] Thaysen regards a rise of less than 40 mgm per cent as a low curve and states that such curves are found in less than 5 per cent of normal individuals Svensgaard[8] Haas[9], McLean and Sullivan[30], Bennett, Hunter and Vaughan[4] and others have found low blood sugar curves in celiac disease with great constancy[31] *The test is very valuable*[30], since it aids in dif



Fig 9 The intestinal x ray pattern in sprue Note the loss of the normal markings of the valvulae conniventes the smooth contours of the intestinal wall and clumping of the barium in elongated masses



FIG 8 The normal x ray intestinal pattern after a barium meal The delicate herring bone markings of the valvulae conniventes (A B) and physiological egmentation are well hown

ances of absorption and evidence of this is supplied by the observations of May and McCreary[47] It would seem a fruitful field for research

Diagnosis

The sprue syndrome when fully developed is characterized by steatorrhea great loss of weight macrocytic hypochromic anemia and a low blood sugar curve after the ingestion of 1 5 gms of glucose per kilo of body weight the values for serum calcium and phosphorus frequently are low and osteoporosis tetany rickets and dwarfism are not rare components of the clinical picture Glossitis and aphthous stomatitis may occur and the skin frequently shows symmetrical patchy areas of pigmentation Essentially the disease is chronic, but remissions and relapses are common No age is exempt though infantile sprue or celiac disease usually begins about the age of two whereas adult sprue shows its highest incidence in middle life Sprue thus is seen to possess definite characteristics which enable the careful observer to differentiate it from other diseases showing more or less marked resemblances to it It has been confused with (1) pernicious anemia (2) steatorrheas due to other causes (3) pellagra (4) the cachexia of malignant diseases and (5) intestinal infections

The clinical pictures of fully developed sprue and of pernicious anemia are so characteristic that only one unfamiliar with the sprue syndrome would be likely to confuse them As Addison pointed out in his original description of pernicious anemia any considerable loss of weight is rare The pernicious anemia patient may show a moderate weight loss but in sprue the loss is tremendous frequently amount to 40 or 50 per cent of the patient s former weight In advanced sprue the patient may be so emaciated that any further loss is inconceivable (Fig 4) and the muscles may be atrophied to such an extent that intramuscular medication becomes a matter of difficulty It is true that sore mouth anorexia indigestion and diarrhea are common in both conditions but the excessive loss of fat in the stools which is the earmark of sprue is not seen in pernicious anemia This sprue steatorrhea is constant and very persistent being found on chemical analysis for some time after clinical cure has been attained The defective calcium metabolism of the sprue syndrome is not encountered in pernicious anemia Furthermore the constant achlorhydria of pernicious anemia is not found in sprue in which indeed the incidence of achlorhydria is only slightly greater than that found in normal individuals The disappearance of the achlorhydria of pernicious anemia under treatment is excessively rare [73] but this is a frequent occurrence in the sprue syndrome in which acid values commonly rise with clinical improvement The blood sugar curve after the ingestion of 1 5 gms of glucose per kilo is low in sprue but shows the normal ele

creased above the normal It would seem that in the sprue syndrome the mechanism for the splitting of proteins into amino acids and for their absorption, is not seriously, if at all, disturbed

Blood Chemistry

The calcium and phosphorus values for the blood serum usually, though not invariably, are low in well developed cases of the sprue syndrome The serum proteins are, as a rule, moderately reduced and may be quite low without, however showing a reversal of the albumin globulin ratio The plasma cholesterol usually is lowered, and the fasting blood sugar is low Blood chemical findings do not show otherwise any characteristic variations from the normal

Basal Metabolism

One might expect that the basal metabolism in sprue would be subnormal, since sprue cachexia presents the picture of starvation Several observers[7 32], however, have reported a rather marked increase in the basal metabolic rate in some sprue patients, the rate tending to fall toward normal figures with clinical improvement We too, have found the basal metabolic rate somewhat elevated occasionally, though rarely higher than plus 30 per cent The phenomenon has never received a satisfactory explanation We have not found determinations of basal metabolic rates of any service in the differential diagnosis of sprue In the large majority of sprue patients observed in the Duke Hospital Clinic the rate has been within normal limits

Roentgenological Findings

Snell and Camp[33] first reported certain changes in the intestinal pattern of the small intestines after a barium meal in the sprue syndrome (Figs 8 and 9) These changes comprised smoothing of the contours of the lumen, obliteration of the herring bone markings due to valvulae conniventes and clumping of the barium in elongated masses With liver and dietary therapy these abnormalities regressed toward the normal intestinal pattern Snell and Camp did not consider that such x ray changes were characteristic of sprue, but state that they are similar to those found in chronic inflammatory lesions of the intestines Other observers[34 35 36] have confirmed fully the observations of Snell and Camp, but the exact significance of the changes noted is not clear though there is a growing tendency to ascribe to such alterations of motility a more important role than was done when the observations were first published It is perhaps safe to conclude that disturbances of the normal motility of the gut might readily cause disturb

hibited marked refractivity to the liver and dietary treatment which in the great majority of patients suffering from the sprue syndrome yields prompt and brilliant results [1] Three of these patients died In other words under certain conditions the morbid process is irreversible The reason for this occasional refractivity to treatment is not known

Treatment

Sprue has been treated in the past by special diets of the most diverse and even contradictory character In 1926 Bloomfield and Wyckoff applied to the treatment of a case of so called tropical sprue the liver therapy which Minot and Murphy had just introduced into the treatment of pernicious anemia Improvement in all the patient s symptoms was prompt and sustained Since then other reports [3 14] have confirmed these results fully It is true that an adequate protein intake with a well ordered general diet in which the fats are restricted will alone control the milder cases of sprue but liver undoubtedly contains certain unknown substances which are essential in the therapy of the severer forms of the disease It is amazing that this vital and easily demonstrable fact should have been so long delayed in influencing the treatment of sprue both in adults and children

The victim of sprue cachexia suffers from almost complete loss of appetite so that the ingestion of an adequate diet is very difficult When liver is given in adequate amounts the appetite is restored rapidly and in a few days the patient who formerly had shown every evidence of di gust for food develops an insatiable appetite A gain in weight of a pound a day is not uncommon A sense of well being replaces the former state of lassitude and depression and a *feeling of strength gradually overcomes the sense of utter weakness* The painful red tongue assumes so rapidly a normal appearance that it may well be regarded as a reliable indicator of the efficacy of treatment The diarrhea diminishes and constipation may develop Flatulent indigestion which is such a distressing symptom of sprue grows less troublesome despite the greatly increased food consumption though some discomfort with short bouts of diarrhea is liable to recur occasionally The stools gradually lose their frothy fatty appearance though mild steatorrhea usually persists for some time

May and McCreary found that celiac disease or infantile sprue responded much better to a not too refined liver extract together with vitamin B complex both given in 2 to 4 c c dosage parenterally on alternating days

Liver therapy in sprue produces the same response in the hematopoietic organs as it does in pernicious anemia Young erythrocytes appear in the blood and the color and volume indices fall to normal as the red cell count rises Iron

ation in pernicious anemia Low calcium and phosphorus values in the serum and osteoporosis and tetany are not found in pernicious anemia, while not an uncommon finding in the sprue syndrome

Spinal cord degenerations frequently are seen accompanying the macrocytic hyperchromic anemia of the pernicious type, but they are rarely encountered in sprue[11] Paresthesias are found quite commonly in both conditions, and the macrocytic anemia of sprue is indistinguishable from that of pernicious anemia The deficiencies underlying both diseases can be replaced by certain constituents of normal liver, but since we do not know the exact chemical nature of the deficient substances the fact that they are contained in the liver is not sufficient evidence that sprue is merely a clinical variety of pernicious anemia

If the pernicious anemia histories of any large clinic are studied carefully instances of sprue probably will be discovered among them Among 77 histories of patients classified as pernicious anemia in the Duke Hospital the writer found the records of three cases showing the presence of free hydrochloric acid in the gastric secretion after histamine stimulation, and all of these could be identified easily from their gastrointestinal histories, low blood calcium values great loss of weight, et cetera as instances of the sprue syndrome

Pellagra is a deficiency state with clinical resemblances to both sprue and pernicious anemia It cannot be diagnosed, however, in the absence of the characteristic skin lesions or of a credible history of these, anemia is not a striking feature and usually is hypochromic in type, though macrocytosis is not infrequent The diarrhea often is severe, but the stools are not fatty or bulky as in sprue Low blood sugar curves are not characteristic of pellagra Severe mental deterioration so frequently seen in pellagra is not characteristic of either sprue or pernicious anemia Pellagra is amenable to nicotinic acid therapy, whereas no results at all comparable to those of liver treatment are seen when pernicious anemia or sprue are treated with adequate dosage of nicotinic acid

Prognosis

The advent of liver therapy has completely altered the outlook in sprue In its milder forms sprue is not a serious disease and its frequent relapses may be so slight that the patient does not consult a physician he merely accepts his fate as a chronic dyspeptic When sprue reaches the stage of cachexia, however, it is a serious menace to life, and it is in these severe forms of the disease that liver therapy may yield its most brilliant results Even the most desperate cases need not cause despair for as Miller and Rhoads[13] have shown, recovery is possible when the patient is moribund

However, among 66 sprue patients treated in the Duke Hospital Clinic 4 ex

day of treatment The condition of the tongue appetite and stools furnishes the best guide to treatment One of the most striking phenomena observed in the liver treatment of sprue is the rapid improvement in the patient s sense of well being This occurs several days before the weight increases or the blood improves and is explained most reasonably by improvement in the patient s general metabolism Complicating diseases especially infections markedly reduce the efficacy of liver therapy

(3) *Vitamins* — The exact relation of the curative substances contained in liver to vitamins still is obscure though there are indications that such a relationship exists, especially with the vitamin B complex Because of the well founded belief that in sprue a deficiency of accessory food factors exists substances rich in vitamins should be added to the diet Orange lemon lime or tomato juice should be given daily and brewer s yeast or autolyzed yeast (vegex marmite) a teaspoonful in a glass of warm water 3 or 4 times daily has proven useful though occasionally it seems to increase the flatulence which is such a common complaint in sprue In the treatment of nutritional deficiencies it is of great importance to realize that the patient is suffering from a generalized deficiency state and that anemia stomatitis and gastrointestinal disorders for example are but the presenting symptoms of an abnormal condition from which the whole body suffers

(4) *Inorganic Salts* — Calcium lactate (1 gm [grs xv] t i d , p c) and viosterol and halibut liver oil (1 c c [mins xv] daily) or a similar preparation should be used to aid the defect in calcium metabolism Certain cases of sprue will require iron in large doses together with adequate amounts of liver extract for their complete recovery since here as in pernicious anemia a double deficiency sometimes exists Finally the great aid to be derived from the intravenous injection of from 300 to 500 c c of blood should not be neglected in beginning the treatment of sprue cachexia

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in large doses will be necessary in some cases to restore the blood to normal It is remarkable how easily a full, generous diet is digested by the sprue patient, when adequate amounts of liver are given Some observers[11] have insisted upon rest for the intestine in sprue It would seem more sensible to permit the starved body to satisfy its needs and thus overcome the deficiency which underlies the intestinal injury Clinical experience supports this point of view Fats must be restricted in the beginning, but as soon as possible they should be restored gradually to the diet A high protein, high vitamin diet is indicated, and upon this the patient thrives Minor relapses should not be taken too seriously, for they are of short duration and grow less and less troublesome as the patient gains weight and strength In the severer cases of sprue many months of persistent treatment may be required to restore the patient to normal health, and in some cases evidence of permanent injury to the intestine may persist

When the serum calcium value is low, calcium salts and viosterol should be used and it is probably true that all sprue sufferers are benefited in the beginning by this treatment[41] Dilute hydrochloric acid is indicated when hypochlorhydria or achlorhydria is found

Sprue varies so greatly in the severity and character of its manifestations that it is always desirable to individualize the treatment However, it may be profitable to summarize the present conception of the essentials (1) The *diet* should be rich in proteins and sharply restricted in fats until the diarrhea is controlled Carbohydrates need not be restricted, though foods containing much cellulose should be passed through a colander Bananas either fresh and well ripened or in the form of banana flour, are well tolerated[3] Skimmed milk defatted buttermilk and cottage cheese may be fed liberally, both for their protein and calcium contents Too much stress has been laid on special diets in the treatment of sprue Under the influence of liver therapy the patients with severest symptoms eat digest and assimilate a generous mixed diet in which fats only are restricted Fats may be added very gradually as the diarrhea improves

(2) *Liver Therapy* — Parenteral administration is the method of choice until the patient can take either cooked liver or crude liver extract (Valentine s) by mouth In beginning treatment the amount of liver extract derived from 100 gm of liver is given each day until the patient s response is satisfactory It cannot be too strongly emphasized that *the amount of liver used must be adequate to control the symptoms* of the disease and this can be determined only by observation The maintenance dose and the manner of its administration, whether orally or parenterally must be determined by careful observation of the individual case When the patient has regained his lost weight and is eating a well balanced diet, liver by mouth twice weekly will suffice Anorexia and sore tongue are the first symptoms to improve, and this occurs as early as the third or fourth

day of treatment The condition of the tongue appetite and stools furnishes the best guide to treatment One of the most striking phenomena observed in the liver treatment of sprue is the rapid improvement in the patient s sense of well being This occurs several days before the weight increases or the blood improves and is explained most reasonably by improvement in the patient s general metabolism Complicating diseases especially infections markedly reduce the efficacy of liver therapy

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Sept 1 1943

CHAPTER XXVII-A

BIG HEEL

(ENDEMIC ENLARGEMENT OF THE OS CALCIS)

BY MAJOR JAMES STEVENS SIMMONS MEDICAL CORPS U S ARMY

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Definition — Big heel or endemic enlargement of the os calcis is a tropical disease of unknown etiology characterized by acute onset with fever accompanied by pain over the os calcis and progressive enlargement of this bone

HISTORY AND DISTRIBUTION

The disease was described in 1904 by MacLean[1] who observed that it was not uncommon among the Wassans a tribe of Fantis living in the Kaziankor region of the Gold Coast of Africa and that it also occurred among Kroos and in a Bassa brought to work the mines from a district on the coast of Liberia In 1905 Maxwell[2] reported finding a somewhat similar disease among the natives of Formosa however the condition described by him appeared to be more chronic and may possibly be different

ETIOLOGY

The cause of Big heel is unknown Biting insects have been suspected but MacLean was unable to find any evidence to support such a theory The disease has been observed most commonly in young adults 18 to 30 years of age and its occurrence seems to be in some way related to the wet season Many of the cases seen by MacLean developed during the rains and one patient with

a chronic condition gave a history of annual recurrences of pain during the rainy season for a period of ten or twelve years

Pathology

Information concerning the pathology of the disease is meager and limited to macroscopic observations which indicate that there is enlargement of the outer surface of the os calcis Either one or both heels may be affected, and in some instances the other tarsal bones are also enlarged However, there is no involvement of the metatarsal bones or of the ankle joint

Symptomatology

The onset of the disease is believed to be abrupt, although a few of the patients have stated that for about three days prior to the acute attack they experienced an itching sensation in the part which later became painful No other prodromal symptoms have been described

The first symptoms include moderate fever extreme tenderness over the os calcis and local pain which may be severe enough to prevent sleep and to interfere with walking Within three to seven days there begins a progressive enlargement of the outer surface of the bone, and this continues for two to four weeks, during which time there is some decrease in the pain, and the temperature may return to normal

After reaching its maximum size the swelling remains unchanged for one or two months the patient suffers less pain and is able to walk This is followed by a period of recovery during which the os calcis gradually becomes smaller, and the pain disappears By the end of the fourth month there is usually no pain or tenderness, and the enlargement is about half as great as at the height of the disease

However the bone may not return to the normal size and in certain cases there is considerable permanent enlargement This does not interfere with function and the patient feels well The other tarsal bones may also be affected but usually the lesions are limited to either one or both heels If bilateral the enlargement is not symmetrical, and commonly, the deformity of the right heel is more marked

As a rule, the disease is limited to one attack but recurrences do occur and these appear to be most common during the wet season MacLean reported that one patient who was subject to recurrences remained comfortable between the attacks provided he did not wet his feet with cold water Apparently the decrease in temperature brought on pain

Treatment and Prophylaxis

There is no known specific treatment for the disease However it is stated that relief may be afforded by cutting into the affe ted area and trephining a hole into the bone

Nothing is known concerning the prevention of big heel

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Jan 1 1933

CHAPTER XXVII-B

AINHUM

By MAJOR JAMES STEVENS SIMMONS Medical Corps U S Army

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Definition —Ainhum a chronic disease observed among negroes East Indians and other dark skinned races is characterized by the slow development of a constricting band around the base of one or more toes usually the fifth which eventually results in spontaneou amputation of the toe

Synonyms —The name ainhum was applied to this disease by African negroes (Nagos) among whom the condition was seen by Da Silva Lima (1867) in Brazil In the Yoruba language ainhum means a saw or file Other synonyms include ainham sukha pakla (India) fadidite (Madagascar) gundu rum excresis spontanea (A Collas) dactylolysis essentialis (G Beauregard) Silva Lima s disease, esola or ombanja (Benguilo West Africa), dactylolysis spontenea

History and Distribution

Cases of ainhum were reported by Clark in 1860 The disease was seen in 1852 by Da Silva Lima who with Wucherer in 1867 described cases among the descendants of African slaves in Brazil The disease is widely distributed and has been found in the negro arab hindu mussulman and the mongolian (Pyle 1893) In Africa it occurs in Algeria Egypt Sudan East Africa Madagascar and the Transvaal, and is prevalent on the west coast particularly in the Gold Coast region It also occurs in India, Ceylon, possibly in China and in Polynesia The disease has been found in the southern United States in the West Indies and in South America where most of the cases have been reported from Brazil the Argentine and British Guiana

INTRODUCTION

"The first step, in order that we should understand syphilis, is to recognize that it is by no means necessarily a venereal disease'

Sir Jonathan Hutchinson (1829–1913)

DEFINITION — Treponematosis may be defined briefly as a universally distributed acute and chronic disease of man known for thousands of years and by many names in various times and places and caused by a fragile spiral parasite of the genus *Treponema* Propagated both through venereal and nonvenereal channels it is characterized by early and late stages separated by a latent period it evokes a characteristic pathological response in human tissues, is diagnosed by special serological tests and is susceptible to treatment with the heavy metals and penicillin

It is a striking feature of treponematosis that, unlike most other diseases, it has been given a multitude of different names This fact is a witness to its universality and is not without some bearing on the nature of the disease So many names have been given it that some writers have called it the 'disease of one thousand names' Certain authors have made collections of these names numbering several hundreds[1] Sometimes treponematosis has been called by descriptive names such as frambesia (raspberry), sibbens (berry), pustulis bubas, pinta, sometimes by transliterated native names such as yaws (Africa), irkintja (Australia) and bejel (Syria) sometimes by fanciful ones like syphilis or the disease of St Job It has been confused with many other diseases, as for example button scurvy scabies grossa variola grossa and venereal leprosy, it has been called the foreign" disease and given the name of innumerable towns and countries, such as morbus gallicus the Neapolitan disease, Amboina pox, mal di Fiume and the Crimean disease It was called skerljevo in Dalmatia, radesyge in Denmark and spyrokolon in Greece Hardly a country in any part of the world but has had its native name for the disease Sometimes it has borne two names simultaneously in the same country one to describe its adult acquired, venereal form and the other for its nonvenereal, childhood acquired form Thus in the Balkans there was syphilis and skerljevo in Australia kirkni and errikincha and among the Arabs franghi and bejel Sometimes a particular manifestation has been dignified with an individual name such as gangosa in Guam and pinta in Mexico

All these names and many others will be introduced in this discussion but they will all be gathered up in the one word treponematosis, a name unconditioned by time or place a name which carries the sole implication of being caused by a treponeme This disease name was introduced into English medical literature

by Butler and Peterson[16] in 1927 and is in line with modern nosology which gives preference, if possible to disease names based upon etiology *Treponema* is the generic name for the microscopic parasite which is constantly associated with treponematosis no matter by which one of the thousand names it may be called *

The Parasite

Treponema was so named by its original discoverer Schaudinn in 1906 and is given the following relationships by Bergey[6]

Order VII *Spirochaetales*
Family *Spirochaetaceae*
Genus I *Spirochaeta* Ehrenberg
Genus II *Saprospira* Gross
Genus III *Cristispira* Gross
Genus IV *Borrelia* Swellengrebel
Genus V *Treponema* Schaudinn
Genus VI *Leptospira* Noguchi

Biologists in the past have been in doubt as to whether the members of this order rightfully belong to the animal or plant kingdom but modern consensus tends to favor the latter In view of this the choice of the non committal terminative osis signifying disease of is to be preferred to iasis which generally infers infestation by an animal parasite

No organism has a more legitimate name than *Treponema* Schaudinn first gave his discovery the generic name *Spirochaeta* but that name as well as his second choice was already preempted (they were homonyms) and he finally coined the new word *Treponema* Meantime the dramatic discovery had publicized the wrong name and unfortunately error once afoot is hard to overtake Now after 40 years there is a definite trend to give *Treponema* its rightful place Its neighbor *Borrelia* also long known as a spirochete had had to contend with the same handicap

The medical profession as a group has clung to the earlier erroneous name *Spirochaeta* whereas zoologists with increasing knowledge of the order have unanimously supported the correct word *Treponema* The two points of view were brought to the fore in 1916 in an interesting interchange between Pusey and Stiles [6] Pusey although admitting that it would be desirable to have every name scientifically accurate contended that the only sanction for a name was usage and since *Spirochaeta* was entrenched in the literature by long usage he

* The editor suggests that at this point the reader turn to page 656 (11) and read the section headed Summary and Conclusion before continuing his perusal of this chapter

resented the attempt of 'systematists' to 'substitute a less familiar name', even if it were established beyond further question that *Spirochaeta* was not scientifically appropriate He claimed that *Treponema* lingered in the literature only where it was maintained through loyalty to the memory of Schaudinn, or occasionally where there was an excessive amount of purism An editorial in the JOURNAL of the American Medical Association[31] added a further touch with the words, 'Sentiment would cling to the term *Treponema* because Schaudinn, the discoverer of the organism, so named it, but sentiment usually does not count in science'

Stiles, however, who was both physician and zoologist, replied that Pusey's point of 'preponderant use' was not well taken, as there are rules of zoological nomenclature, international in character which are the best guide to scientific usage He advocated *Treponema* not out of deference to Schaudinn, but because it was in accord with the international rules, which do not recognize a question of sentiment Stiles contended that this was not an editorial question but one to be decided on the basis of the biological classification of the genera concerned

Pusey retorted that Stiles argument represented a 'medieval worship of authority' and seemed unconscious of the authoritarian nature of his own point of view Much of Pusey's argument has faded with the years, and time is proving him wrong in his prediction that *Spirochaeta* will continue to be the generally used name for the organism of syphilis

Editorial policy has to bear much of the burden of responsibility for the perpetuation of *Spirochaeta* in medical literature In the symposium on syphilis organized by the Medical Section of the American Association for the Advancement of Science in 1937 several authors were required by 'policy' to change their manuscripts substituting *Spirochaeta* for *Treponema*, although this organization of scientific medicine might be expected to take the lead in correct nomenclature The publications of the American Medical Association have long been sturdy contenders for *Spirochaeta* but the unvarnished word *Treponema* has at last appeared even in the pages of the JOURNAL (Nov 6 1943)

Many clinicians still prefer *Spirochaeta* although the more scientifically minded such as Stokes[11] admit that *Treponema* is the correct name of the genus Stokes, however, falls back with Pusey on 'usage" as an argument for the retention of the obsolete name, apparently unconscious of the fact that he and his editorial and professorial confreres are largely responsible for that usage and could correct it in a few generations of medical students Textbooks, however, such as Cecil and Christian's edition of Osler, use *Treponema pallidum*

Not that anyone would wish to obliterate the historic word spirochete The colon bacillus will still be accused of an odor though its name is now *Escherichia coli* and the pinworm is the same whether *Oxyuris* or *Enterobius* So let the

spirochete remain in clinical medicine as a synonym of treponeme and spirocheto sis as a synonym of treponematosis only let it be clear that these words are historic relics used in a familiar sense and in disregard of correct taxonomy This is the sense in which they will be used herein Treponematosis however is the precise scientific name for the disease discus ed in the following pages For those who like scientific precision its etiological agent is the *Treponema*

The treponeme has a length of 4 to 10 micra with an average of 7 It has the form of a drawn out spring usually with 3 to 12 coils although in unusual cases *they may number more than 20 The thickness of the filament is 0 25 micron* Reproduction is by transverse fission and there is no alternation of genera tion There is a characteristic motility compounded of combinations of three components viz translation in the long axis a corkscrew rotation about the axis and a waving or twisting motion [3] The motility is the same whether the trep oneme is from an empeines lesion of pinta the bubas of Haitian yaws or the chancre of a Viennese clinic The morphology is the same whether the treponeme is from a case of parangi in Ceylon of *bejel* in Syria of paresis in *Baltimore* or of aortitis in Warthin s pathological sections As Bessemans says the treponeme is and remains a treponeme

As to viability the treponeme is a very fragile creature unfavorably affected by many common agents A temperature of 45 C just above fever heat will kill it within 10 minutes and for the treponeme to dry is to die The weakest antiseptics will kill it and a soap solution is even quicker in action than many disin fectants [17] It cannot even endure in tapwater These facts have a direct bear ing upon its behavior in man its obligate host Although it may be introduced experimentally into a number of animals there are no true vectors in nature and no alternative or reservoir hosts Stokes[11] regards the relation of treponeme to man as easily one of the sovereign instances of parasitic adaptation in the entire field of disease

Something in the very nature of host tissue seems to be necessary to maintain the virulence of treponemata for all attempts to culture it in artificial media have resulted in a harmless non pathogenic saprophyte It is possible to speculate with Bessemans[7] that it may have originated in some saprophytic form Most of its relatives of the Family *Spirochaetaceae* are saprophytes and it may be that once introduced into man it found in the primate tissues some biochemical factor inter action with which brought forth the characteristic pathogenesis of trepone matosis Its uniform reversion and resumption of its saprophytic nature in cul ture media is certainly harmonious with this view

Rolleston says that bacteria can and do undergo evolution from a saprophytic to a pathogenic state As Adami says It is absurd in these days to imagine that the infections have always been with us absurd to imagine that when the

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Eastern bridge and carried their treponemes with them to India the East Indies the Islands of the Pacific and Australia From Burma and Indo China a branch went north through China to Mongolia across the Aleutian bridge to North America *and from thence to Central and South America*

As a result of these migrations treponematosis was established in Ceylon and the moist hot zones of India and it established itself in the East Indies and the Pacific Islands That there should be such a striking similarity between the infection as seen today in tropical Africa and in the far islands of the Pacific is *explained by Hamlin on the well established zoo-geographical principle* that the earliest types of the more primitive peoples of the world are to be found today in so-called survival or refuge areas whither they have migrated or been driven Mumford says that yaws is known to have been widely distributed in many of the Pacific Islands at the time of their discovery by white explorers Yaws says Hamlin was endemic in Melanesia and Australia long before the age of maritime adventure [it] is undoubtedly an old disease in certain parts of Polynesia but it is much older in New Guinea The distribution of treponematosis *in the Eastern Hemisphere predicates that an archaic representative of the disease* was associated with the Polynesian migrations into the Western Pacific These migrations of the Polynesian races cannot be dated but their linguistics and ethnology bear witness to great antiquity and yaws is the only Polynesian disease that can be linked with the voyages outward from the center at Tahiti [2]

As long as treponematosis remained in the moist tropical zones such as Central Africa and the Pacific Islands it retained its character as a childhood disease untreated unisolated and affecting everybody in the primitive villages This type of treponematosis did not start with a chancre but with a florid skin eruption it did not end in aneurysms and paresis but in gangosa pinta-depigmentation skin ulcers and periosteal gummata The climate was warm enough and moist enough for treponemata to live and multiply on unclothed human skin as well as within the dermal layers the blood vessel walls and the bones The skin lesions burgeoned *in profuse and succulent papillomata whose serous secretions* poured out a continuous bath of treponemes upon the skin This with variations from country to country due to local environmental conditions was the general picture of treponematosis in the pastoral and agricultural communities lying within the isotherms of 80 F in areas of lush vegetation and a rainfall of at least 50 inches per annum It is the picture one sees in such areas today

There were some areas of the tropics however which were dry rather than moist cool instead of hot and in these areas the external appearance of treponematosis changed considerably *In cooler and dryer climates the human skin* surface offers unfavorable conditions for life and propagation of the treponeme Sometimes there is a seasonal swing and the treponeme can persist on the surface

woman gave the man the fruit of the tree he acquired the germs of all bodily ills We see how from time to time infections or epidemic diseases may arise de novo through the evolution of more specialized pathogenic forms from the more widely diffused saprophytic micro organisms growing upon the surfaces of the body'

Historical Review

> If there was ever a medical question which deserved to be looked at with historical perspective this question of yaws and syphilis is that one"
>
> Charles S Butler[1]

Two things seem certain one that it was in the remote and unknown past that the treponeme first established itself as a parasite of man and the other, that it must have been in some moist hot climate, conducive to the existence of the fragile spiral, that it first found lodgment on the skin of man and made its way through some adventitious opening into his tissues One cannot say of course where this event took place, but Manson and many others mention Africa as the probable original home of treponematosis (yaws) Certainly equatorial Africa offers the required climatic conditions, and Hamlin[53] adds the anthropo logical observation that long standing endemic foci of treponematosis exist among the most primitive and sedentary tribes of Africa today, its deforming processes being recognized in their archaic languages and customs Yaws is a native African word and its reduplicated form ya ya turns up in the Caribbean as an inheritance of African slave days One sees in the native African today a complete and de tailed picture of the juvenile and rural treponematosis which resulted from that first chance encounter Much of the disease, as it affects man today, conforms to this primitive epidemiological pattern of the unclothed native, ignorant of isolation and treatment, of moist skin humid heat and physical propinquity beyond imagin ation, of flying, hopping and crawling ectoparasites to serve as passive vectors and scratches and other traumatic accidents of the jungle to provide a multitude of portals for entry

The Proto negroid Migrations

Hamlin[53] says that primary diffusion of treponematosis probably occurred over a long period during the paleolithic period Africa was at that time the hu man reservoir out of which migrations came and there were two streams rising from this source The lesser kept on northward across Europe as far as the Baltic, but the main flow of Proto negroid migration turned eastward across the Near

more substantial and cleaner dwellings and were not subject to the traumata of jungle life nor the attacks of such a multitude of insects The surface temperature of these people conforming to their environment was lower and the skin surface dryer The body to body contacts among the children were less and the practice of bathing was increased Thus treponematosis as an exanthem of childhood tended toward extinction

If treponematosis had been a mere skin disease its extinction might have been total but being a constitutional disease caused by a versatile parasite it merely changed its angle of attack from a pattern of juvenile nonvenereal disease to one of adult venereal infection In the primitive African villages so long as all the children acquired the disease from each other promiscuity among the adults had no bearing on the course of the disease but as the juvenile form faded the adult form with its basis in promiscuity came to the fore The force of environmental factors made it more difficult for the treponeme to persist on the skin and drove the eruption toward the mucosae of the mouth and vagina Thereupon sexual intercourse became the prime human act of sufficient intimacy to provide a clear channel for infection and thus came about the biological accident of which Stokes says It is not a divine moral purpose or a satanic primitive ingenuity that connects syphilis with genital activities but a mere biological accident no more significant in the last analysis that the fact that potatoes grow in sandy loam [117]

In the development of treponematosis as a venereal disease new economic and social factors appeared For the people of the temperate zones were aggressive their standards of living rose the number of their material desires increased their social structure became more complex An inevitable result of this social evolution was a rise in the dignity of the marriage relation on the one hand and on the other the development of a prostitute class for entertainment purposes This was the evolutionary course of venereal treponematosis (syphilis) in the temperate zone and every step in the process can be demonstrated today as now here now there some segment of the human family rises from uncivilized to civilized levels through economic and sanitary improvement The flow is for the most part from the juvenile to the adult form from the nonvenereal to the venereal because that is in the direction of social evolution but there have been enough instances of temporary ebbing i e reversion from venereal to nonvenereal to serve as controls

As in all such changes in nature a period of transition is recognizable and something should be said about the characteristics of this transitional treponematosis which lies evolutionarily speaking between the primitive juvenile disease and the highly specialized venereal disease of Europe and North America Its transitional nature is revealed both in its epidemiology and its pathology Genital chancres are rare and extragenital acquisition still is common Although not so universal in the community as the juvenile form was a large proportion of the

only during the rainy season, as Chambers has described in Jamaica [1] In any event when circumstances discouraged the appearance of treponemata on the skin of the trunk, they appeared more abundantly on the skin of the axillae, popliteal spaces, perineum and external genitalia Lesions of the mucous membranes, which were rare so long as the skin lesions were florid, now became more numerous appearing as mucous patches, snail tracks or kidney shaped ulcers on the fauces, palate or pharyngeal wall Such was the treponematosis of desert and mountain areas In Arabia, for example, Thoms today (personal communication) finds a disease of this kind among the Arabs of the desert oases Belesh is the general name for it in all its stages sauda (dark) is used for the early, slightly pigmented warty eruption on the skin 'which so closely resembles the raspberry like exanthem of yaws', and which is accompanied by lesions of the mucous membranes of the mouth, shajar (tree) is used for the serpiginous and circinate late cutaneous manifestations Here in the heat of the date palm groves there is still sufficient moisture on the skin for the persistence of cutaneous lesions, but the treponeme s focus of activity has gravitated to the folds of the body, where the sweat glands are more numerous and to the orifices, where moisture is more constant Papillomata tend to be grouped around the sources of moisture, as the lips the vagina and the anus, not because the parasite " chooses " these areas, but because they constitute for it zones of survival So common is this phenomenon of the lesion ringed about the mucocutaneous border that some writers have even claimed that mucous membrane lesions always arise in and come from the skin across the border As we shall see, this has no diagnostic significance, since the reciprocal relationship of skin and mucous membrane lesions in treponematosis is present in a complete gradation, from the skin rich mucous membrane poor pattern to one exactly the reverse, depending on the heat and moisture of the environment and varying with the season and climate

Ramsay in Assam[1 4] made the observation 20 years ago that heat and moisture but principally the former, appeared to be the main factors in producing the characteristic lesions of treponematosis in his area He noted that the natives of the cooler mountainous areas had fewer and dryer skin lesions Sellards[11] quotes Pick's experience in a mountainous area of the Philippines in a spot where 69 per cent of his cases were under 11 years and where the lesions of 2 800 treated cases were limited largely to the mouth anus and vulva with but few granulomata occurring on other portions of the body

Treponematosis however, did not remain exclusively in torrid zones It went north with the migrations into Europe and turned in the same direction with the human current from India into China, and now it underwent a metamorphosis already foreshadowed by its behavior in the desert and mountainous areas of the tropics For these people of the temperate zone wore clothes, were housed in

more substantial and cleaner dwellings and were not subject to the traumata of jungle life nor the attacks of such a multitude of insects The surface temperature of these people conforming to their environment was lower and the skin surface dryer The body to body contacts among the children were less and the practice of bathing was increased Thus treponematosis as an exanthem of childhood tended toward extinction

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In the development of treponematosis as a venereal disease new economic and social factors appeared For the people of the temperate zones were aggressive their standards of living rose the number of their material desires increased their social structure became more complex An inevitable result of this social evolution was a ri e in *the dignity of the marriage relation on the one hand* and on the other the development of a prostitute class for entertainment purposes This was the evolutionary cour e of venereal treponematosis (syphilis) in the temperate zone and every step in the process can be demonstrated today as now here now there some segment of the human family rises from uncivilized to civilized levels through economic and sanitary improvement The flow is for the most part from the juvenile to the adult form from the nonvenereal to the venereal because that is in the direction of social evolution but there have been enough instances of temporary ebbing i e reversion from venereal to nonvenereal to serve as controls

As in all such changes in nature a period of transition is recognizable and *something should be said about the characteristics of this transitional treponematosis* which lies evolutionarily speaking between the primitive juvenile disease and the highly specialized venereal disease of Europe and North America Its transitional nature is revealed both in its epidemiology and its pathology Genital chancres are rare and extragenital acquisition still is common Although not so universal in the community as the juvenile form was a large proportion of the

only during the rainy season, as Chambers has described in Jamaica [1] In any event, when circumstances discouraged the appearance of treponemata on the skin of the trunk they appeared more abundantly on the skin of the axillae popliteal spaces perineum and external genitalia Lesions of the mucous membranes, which were rare so long as the skin lesions were florid, now became more numerous appearing as mucous patches snail tracks ' or kidney shaped ulcers on the fauces palate or pharyngeal wall Such was the treponematosis of desert and mountain areas In Arabia, for example, Thoms today (personal communication) finds a disease of this kind among the Arabs of the desert oases Belesh is the general name for it in all its stages, sauda (dark) is used for the early slightly pigmented warty eruption on the skin ' which so closely resembles the raspberry like exanthem of yaws ", and which is accompanied by lesions of the mucous membranes of the mouth, shajar (tree) is used for the serpiginous and circinate late cutaneous manifestations Here in the heat of the date palm groves there is still sufficient moisture on the skin for the persistence of cutaneous lesions, but the treponeme s focus of activity has gravitated to the folds of the body, where the sweat glands are more numerous, and to the orifices, where moisture is more constant Papillomata tend to be grouped around the sources of moisture, as the lips the vagina and the anus, not because the parasite chooses " these areas, but because they constitute for it zones of survival So common is this phenomenon of the lesion ringed about the mucocutaneous border that some writers have even claimed that mucous membrane lesions always arise in and come from the skin across the border As we shall see this has no diagnostic significance, since the reciprocal relationship of skin and mucous membrane lesions in treponematosis is present in a complete gradation, from the skin rich mucous membrane poor pattern to one exactly the reverse depending on the heat and moisture of the environment and varying with the season and climate

Ramsay in Assam[1 4] made the observation 20 years ago that heat and moisture but principally the former, appeared to be the main factors in producing the characteristic lesions of treponematosis in his area He noted that the natives of the cooler mountainous areas had fewer and dryer skin lesions Sellards[11] quotes Pick's experience in a mountainous area of the Philippines in a spot where 69 per cent of his cases were under 11 years, and where the lesions of 2,800 treated cases were limited largely to the mouth, anus and vulva with but few granulomata occurring on other portions of the body

Treponematosis however did not remain exclusively in torrid zones It went north with the migrations into Europe and turned in the same direction with the human current from India into China and now it underwent a metamorphosis already foreshadowed by its behavior in the desert and mountainous areas of the tropics For these people of the temperate zone wore clothes were housed in

traordinary proportion of extragenital infections in Czarist Russia In some areas they far out numbered the genital and he put this fact down to the close contact of the peasants on the stove where they were accustomed to sleep in winter

In recapitulation it will be noted what a crucial role cleanliness has played in the evolution of treponematosis from the juvenile nonvenereal form to the adult venereal form In the words of a report of the Medical Department of Kenya[47], The adoption of cleanliness even in small degree appears no less potent against the incidence of yaws than bismuth or arsenic therapy Basedow writes from Australia What immeasurable amount of good a bar of ordinary soap could do *among the wretched multitude of natives afflicted with yaws* [3] *In contrast to this* it will be noted what a perfect medium was discovered for the treponeme in sexual intercourse a channel of propagation immune to scrupulous soap and water ritual and effective in the most polished civilization

Treponematosis and Black Slavery

From very early times slaves were captured in Central Africa for sale in North Africa and the countries of the Mediterranean We have no record of treponematosis among these unfortunates but we can judge by analogy with those which were taken from the same region to the New World that they must have carried with them a constant infusion of treponematous infection The old slave routes may be traced today from Central Africa north from Timbuctoo Lake Chad Kuka Kano Katsina the Sudan and the upper bend of the Niger[1 7] The Arabs were inveterate slavers and the word, coffle which came to signify the slave gang is a transliteration of the Arab word for caravan Scott[111] says Slaves were imported into Lower Egypt in the early dynasties they made up a considerable proportion of the population of Greece and Rome after the Mohammedan Conquest of Africa they were brought from the Sudan Abyssinia and the Zanzibar Coast to Northern Africa Arabia Turkey and Persia Hebrews Babylonians Greeks and Romans all make frequent references to slaves from Africa and the trade which procured them from Ethiopia and from East and Central Africa There was also slavery within Africa itself[1 7] A heavy influx of slavery travelled with the conquering Arabs along the southern Mediterranean littoral from East to West into Morocco and overflowed with the Moors into Spain For over 200 years the Spanish Moors continued to import black slaves from across the Straits

Then the Portuguese explorations of the African coast began scarcely less important than the discovery of the New World and perhaps a prerequisite to that event Marco Pizziani sailed south along the coast in 1367 and for many years Portugal sent vessels farther and farther until Gil Eamus rounded Cape Verde in 1434[94] Within a few years ships had gone far enough to capture negro slaves

population is infected Treatment begins to be instituted but is limited in scope and often ineffective Lesions of skin and bone, frequently resulting in great mutilation, predominate, but vascular disease begins to appear, sometimes terminating in aneurysm Lesions of the central nervous system rarely, if ever, appear Infections of the children are of two sorts, if there are insanitary practices such as prechewing of infant food, or if there is a reversion of the family to the hygiene of the African hut, the acquired treponematosis of childhood will predominate, on the other hand, prenatal syphilis appears, as women, who have escaped treponematosis in childhood, acquire it in adult life and begin to produce children infected in utero

It was this transitional treponematosis, which obtained in China and Russia in early times and which still persists in those countries to a considerable degree Emerson (personal communication) said after a visit to China that he realized that syphilis , as we know it, is an " American " disease Maxwell[84] says that yaws is being continually imported into North China, and that, although syphilis there is extremely prevalent, presenting bone affections very commonly, it nevertheless produces remarkably rare cases of tabes and paresis He also says that, owing to the lack of ordinary cleanliness and of the most elementary treatment, primary venereal sores sometimes assume most bizarre forms and may lead to an appalling destruction of tissue

Capper[18] quotes Gardy, who made a compilation of Chinese medical works the oldest of which dates back 17 centuries before the Christian Era He says ' The descriptions in these works of chancres, of ulcers of the genital organs in man and woman of lesions on the breast, mouth nose and anus are so perfect that no doubt is left in one s mind that they were of syphilitic nature ' Wong[13] states that chancres were mentioned as early as the 7th Century A D , and chancres following intercourse were recognized and described in 1194 and in 1335 but the relation between genital sores and skin eruptions was not recognized Mercury was used in China as early as the 7th Century, fumigations long antedating their use in the Near East and Europe

In Central Europe and Russia have appeared many illustrations of transitional treponematosis which will be discussed below under the heading of the syphiloids ' One will here suffice, the custom syphilis ' of rural villages in southern Ruthenia and the Ukraine so called because the infection was recognized to be conveyed through certain community customs such as kissing the ikon, promiscuous kissing at Easter, feeding babies on prechewed food and the use of common cups and utensils[49] In 1920 a survey was made which showed that 80 per cent of the population were affected, men, women and children Twenty two years later a re survey showed that custom syphilis had vanished with the harmful customs which caused it Finger[113] used to insist on the ex

doubtless many extragenital infections especially among the lowly Certain seasons of the year were warm and moist enough to encourage the parasites to persist on the skin yet the economic standards of the people favored an ever increasing amount of sexual promiscuity and general cleanliness favored genital over extragenital infections Eruptions and sores, bone lesions and depigmentations were frequent but cardiovascular accidents were rare and disease of the central nervous system almost unknown as may be seen today described by MacQueen [3] in Palestine Lacapere in North Africa Von Duhring in Turkey and by many others This was the treponematosis of the ancient Mediterranean world and it is not surprising that Bloch Pusey and others defining syphilis in the narrow terms of the disease as they saw it in their consultation rooms could find none in the ancient world It should be apparent that one would look in vain for a constitutional disease of three stages initiated by venery the usual definition of the syphilitic syndrome in a population many of whose adults had their treponematosis in childhood and whose concepts of the classification and causes of disease were very primitive as will now be shown

Treponematosis in the Light of Ancient Medical Concepts

' In all our thoughts we think in terms of our own social environment

Boas

In reviewing the ancient history of medicine the physician of today must disengage himself from many of the assumptions which he now considers axiomatic Much of the comment on ancient medical writings shows a failure to do this One of the modern fundamentals which must thus be shelved in order to understand these writings is the concept of infection and etiological agent The Chinese looked upon wind cold dryness moisture the affections and suffering poisons evil spirits and imaginary animals as causes of disease[67] In India a form of treponematosis called elephantiasis was considered divine punishment for unchastity The Hippocratic collection lacks any complete or ordered classification of the varieties of disease this early master grouped diseases on the basis of the most prominent symptom Ancient writers described 26 varieties of fever 8 of jaundice 18 of leprosy 15 of ulcers 8 diseases of the throat etc Celsus [5] spoke of penile ulcers some clean and dry others moist and purulent He also spoke of the reluctance which people including the doctors of his day showed toward discussion of genital diseases the first indication of shame as a feature of treponematosis a significant indicator of venery

Manson and others[63] thought that the Biblical disease called blains (Exodus IX) may have been yaws Antyllus[9] in the first half of the 2nd Century

and for the following 350 years Europeın commercial relations were mainly con fined to the trade " Prince Henry, the Navigator, reached Cape Verde in 1445 Sierre Leone in 1461 and the Equator in 1470[1 7] The Portuguese formed per manent settlements at several points along the coast Traffic was in gold dust and slaves and the coast between the Senegal River (17° N) and Benguella (13° S) became the market place Under Henry a regular slave dealing company was organized in Lagos, Portugal, within 10 years there were 1,000 black slaves in Portugal and their numbers increased rapidly Many were exported to Spain[1 7]

The commerce with Africa was a crown monopoly " Every spring fleets of caravels were bringing into the Tagus bags of pepper, cords of ele phant tusks coffles of negro slaves and chests of gold dust Along the quays and in the narrow streets of the old town all the languages spoken from Iceland to the Cameroons could be heard, seamen from Scandinavia, England and Flan ders jostled Spaniards Genoese, Moors, Berbers and converted negro poten tates '[94] In June, 1482, Diogo Cao passed the Equator, discovered the Congo and reached St Marys 13° 26 South Speed in these ships (the caravels) was all important because the Guinea traders usually brought home a 'perishable cargo ' which had to be fed and watered In 1478 35 vessels made the voyage to the Gold Coast Bartholomew Diaz sailed from Portugal in 1487, rounded the Cape of Good Hope and returned in 1488 from a voyage of 12,000 miles Colum bus saw his ships come in[94] Just 10 years later Columbus, off on his own dis coveries stopped at the Cape Verde Islands When he inquired about the slave trade which was brisk in the Islands he was told there was much demand from Castile Aragon, Portugal, Italy and Sicily[84]

In other words, since recorded history began and right up to the time of Co lumbus, African slaves had been infiltrating east into Babylonia, Persia and Arabia north into Egypt and Morocco and across the Mediterranean to Turkey, Greece Italy, Sicily France Spain and Portugal, and the source of these slaves was that same Central and West Africa which is recognized as the probable in digenous home of treponematosis and the exact place from which treponematosis (yaws) was carried by the black slaves to the New World

A very large percentage of these slaves when they left their homes were in fected with treponematosis of the juvenile type as are the present day inhabitants of those regions Since those with mutilating lesions would be undesirable it may be concluded that those selected for export were adults in the latent phase of the disease These could become infectious through mucocutaneous relapse, a phe nomenon to which untreated nonvenereal treponematosis is liable Undoubtedly therefore the stream of slaves was constantly bringing new increments of trep onemes into the population of Mediterranean and Near Eastern countries The result in this population was the transitional type of the disease There were

Evil Eye first recognized on the Euphrates was universally admitted[1] Authoritarianism held medical thought in a tight grip The object of medical study was not observation of the patient but interpretation of the ancient masters A severe pestilence, claiming innumerable victims ravaged the Byzantine Empire in the time of Justinian and although several historians noted it not a medical writer mentions it or describes a case They were not interested in clinical medicine During the Dark Ages quackery was dominant and charms amulets and relics, combined with injunctions to bear pain were the principal forms of medical treatment[14] Yet Pusey and others have insisted on having descriptions of hard chancres and syphilitic syndromes as proof that venereal treponematosis (syphilis) was there at the time and Adami[1] surprisingly remarked Galen is absolutely silent as to the eminently characteristic symptoms of locomotor ataxy and general paresis of the insane There could be no more authoritative evidence that the disease as we know it did not exist in Ancient Rome Syphilis therefore originated or reached Europe at some later period Yet it was not until 1852 that paresis was bracketed with syphilis and tabes was not related to the syphilitic syndrome until 1860[1] Even as late as the end of that century men were still arguing about it L Gluck in 1896 joined those who opposed the syphilitic origin of tabes because he had seen syphilis in the Balkans for 15 years and no tabes and von Duhring[1] in Turkey said for the same reason that tabes could not be syphilitic Others similarly disputed the relation between paresis and treponematosis In other words the absence of descriptions of tabes and paresis in Galen s time is no evidence of the absence of treponematous infection The words of Adami s statement which need to be underlined are as we know it Treponematosis of the juvenile and transitional types were there in Galen s time just as they are today in the Balkans Turkey Syria and North Africa and these types do not lead to neurosyphilis Tabes and paresis are characteristic of the purely venereal adult type of treponematosis as we know it in highly civilized countries

Leprosy and Treponematosis

The twin concepts of contagion and infectious agent it is true were not firmly established until Fracastoro wrote *De Contagione* in the 16th Century yet their adumbrations can be traced in Arab medicine Rhazes (about 900) described smallpox and measles[14] Along the Euphrates we come early upon the concept of a chronic rarely curable disease characterized by cutaneous changes and capable of transmission to others [119] This was called issubu the curse and was isolated The Caliph Al Walid segregated lepers in 707 [4] References to this disease in subsequent centuries are translated by the word leprosy ' in

described the treatment of aneurysm and differentiated between true and traumatic Aetius[97] opposed operating on any aneurysms except the traumatic variety The Plinys, Elder and Younger, in the first Century A D described venereal ulcers on the genitalia, gangosa like conditions of the face called mentagra and eruptions called boas[45] Galen the great clinician, said fever was due to blocking of the arteries, local inflammation or corruption of the humors Brain secretes phlegm (mucus) and semen he said Intestinal worms were said to be formed from putrefying material salivation and dermatoses were attempts by the body to rid itself of internal poisons Urine was secreted from the vena cava, as the abdominal aorta was called[47]

A mind cramped by such concepts could not be expected to unravel the story of treponematosis, sometimes a childhood eruption, sometimes a venereal disease, sometimes acquired, sometimes congenital, a disease characterized by long periods of latency and apparent health, alternating with huge ulcers of the trunk, erosion of the nose and extensive loss of skin pigment Yet Galen's writings dominated medicine for more than 1 000 years

Arab medicine, which took up the torch from the Greeks, assumed disease to be derangement in the action of four elements (earth, air, fire and water) and four natures (heat cold, dryness and moisture) Their whole system was based on a rudimentary anatomy an obsolete physiology and a fantastic pathology[14] Medieval science had two peculiarities 1) solidarity and interdependence of all its branches, such as astrology, music, mathematics and even ethics, metaphysics and politics, and 2) the dominance of certain numbers In illustration of the second point there were four properties of nature 4 elements 4 humors, 4 seasons, 4 winds, 4 ages of man, 5 external and 5 internal senses 7 planets, climes days and seas and 12 months and zodiacal signs A bilious person was " hot and dry ", a phlegmatic ' cold and moist ", a sanguine ' hot and moist ', etc The four humors were blood mucus yellow (liver) bile and black (splenic) bile[14] Humoral pathology was developed on the banks of the Euphrates, where treatises were translated through Syriac into Arabic by Persian doctors under the patronage of Arab caliphs Schools grew up at Armid, Nisibin, Edessa, Damascus and Baghdad and Arab Medicine flourished in the 9th 10th and 11th centuries[119]

As Arab medicine declined in the East the school at Salerno gained in influence, there was a rejuvenescence of Arab medical science in Spain at Toledo, which presented Aristotle and Galen first in new Arabic Persian dress and then in vulgate Latin Saracenic medicine with its Greek inheritance and its crude fumblings for scientific truth thus dominated the Mediterranean up to the establishment of medical education in Europe in the 13th, 14th and 15th centuries

Greek medicine was blind to the fact of contagion Superstition in medicine attained enormous proportions in imperial Rome The baleful influence of the

Scott[110] says 'the term lepra does not convey to us the same meaning that it did to the authors and readers of the earlier writings Even up to the 16th Century and after almost all cutaneous disease characterized by scaly eruption or ulceration might be included in the term It was used sometimes as a generic term for any infectious disease Much doubt is thrown upon the diseases of the patients in the leper houses The diagnosis was made by barbers porters monks and other non medical groups According to Fracastoro writing in the early 16th Century an inspection of leper houses showed only a minority of true lepers among the skin cases

That leprosy was confused with treponematosis is evident from many contemporary writings An edict of 1346 in London[11] states that lepers by carnal intercourse with women in stews do o taint persons who are sound both male and female to the great injury of the people dwelling in the aforesaid city and to the manifest peril of other persons to the same city resorting Another states But there are divers manners of Lepers but it seemeth that the Writ is for those Lepers who appear to the sight of all men that they are Lepers by their Voice and their Sores and the Putrefaction of their Flesh and by the Smell of them As recently as 1839 Maxwell wrote Both yaws and leprosy are possessed of an identity of phenomena closely allied to each other the one is the immediate offspring of the other He thought the virus of yaws undoubtedly possessed the power of producing leprosy

The venereal transmission of leprosy was generally recognized and came to be admitted in the centuries of the Crusades and the protracted European wars which followed the alternative terms of variola grossa or the great pox (pocks) and gros mal came in during the 14th Century In 1463 a courtesan said she kept off an unwelcome client by telling him she had gros mal and in the same year reference is made to le gros mal in a court in Dijon[118] Sometimes this venereal treporematosis was called scabies grossa recognized by its cure with Saracen ointment mercury Holcomb[6] mentions an incident reported in the 14th Century wherein a man lay with a woman who was being treated for leprosy thereupon she became pregnant and he became leprous Theodorus (1 05–1 96) said leprous women were venereally contagious

The general hygienic conditions of the medieval towns with their dense populations their architecture excluding both light and air their narrow streets their defective drainage bad water supply unhygienic burial system etc were the most unfavorable possible the active mercantile and pilgrim intercourse the beggar nuisance the drunkenness and sexual excess the universally prevalent dirt (produced) epidemics and endemics of every kind with great mortality [7] Insufficiency of ordinary foods lack of vegetables unwashed state of bodies sleeping at night in clothes worn during the day the total neglect

English but there is no justification for reading into that word the precise meaning it has gained since Hansen discovered *Mycobacterium leprae*, and the characters of that specific disease were established The inclusive word for the undifferentiated skin disease will, therefore, in the succeeding discussion be 'quoted' It included psoriasis scabies, eczema, lupus and the eruptions of the acute and chronic contagious diseases

As long as 3 500 years ago the Babylonians used positive prophylaxis against leprosy and throughout ancient medicine the idea grew that leprosy, also known as elephantiasis graecorum or in Arabic as baras, was unclean and should be excluded from the community[11] True leprosy may have originated in Africa, where there is today a huge endemic focus Scott[111] attributes leprosy to the African equatorial belt and Saunders[1] says 5 per cent of the natives are infected in some areas There is general distribution throughout India and China with large foci in the East Indies and the Pacific Islands Leprosy was endemic also about the Mediterranean and in Europe and still persists to some degree in those regions In other words, leprosy and treponematosis in ancient and modern times covered much the same geographical distribution We differentiate them today although ofttimes with difficulty In former times however, they were hopelessly confused with each other and with other chronic skin diseases, and this diagnostic catchall was called 'leprosy'

Butler[1] Chambers and others have suggested that the skin disease with whitened hairs described in Leviticus as leprosy was in reality caused by *Treponema* Phoenician traders brought leprosy to Spain and Portugal Pompey's soldiers returning in 62 B C brought it' to Rome From Rome leprosy may be traced to Germany at the end of the 2nd Century, to Spain in the 5th and 6th and thence to France in the 8th Century via the Spanish Saracens[111] Romans brought it to Britain The first mention of leprosy in Ireland was in 432 The first leper house' appeared in England in the 7th Century in Ireland in 869 in Wales in 950[11] The Council of Orleans enacted a leprosy decree in 549, the Council of Lyons in 583 and the edict of Rotharus appeared in 644 The Acts of Charlemagne mentioned it and in 1179 the Third Lateran Council promulgated arrest isolation camps and civil and religious excommunication[119] As early as 1419 leprosy was common among the Portuguese in Madeira and very prevalent in Portugal itself leprosy was rife in Normandy[111] It is said that there were 20 000 lepers in Europe at its height and the system of isolation was enforced mercilessly for centuries with perfect success[110]

Leprosy' has been known in China for 5 000 years but the descriptions have been so comprehensive including disfigured face raucous voice nasal deformities ulcers and mutilations that the term obviously has included a variety of other conditions, among them treponematosis [3] As to its use in Europe

in first place in all three categories as the disease most likely to be mistaken for leprosy[115]

Syphilis as Hutchinson said may imitate all known forms of skin disease but can produce nothing pathognomonic All the known names for skin diseases may in turn receive the adjective syphilitic before them When they do so that adjective becomes of course all important and wholly swamps the designation to which it is appended Not only variola of the exanthemata but varicella, rubeola and scarlatina may be thus imitated Forms of inflammation exactly like those called lupus are very common as the result of syphilis and it is the same with alopecia leucoderma true leprosy and many others We see here the importance of a correct appreciation of a patient s history [0] At another point Hutchinson remarks on the confusion between syphilis and neuralgia apoplexy, hemiplegia epilepsy rodent cancer of the face drugs such as copaiba generalized rheumatism and even quotidian ague He says The different types of syphilitic eruption never prevail epidemically but as it were quite by accident The rare ones are equally rare and the common ones equally common, at all times and in all places they depend on the idiosyncrasy of the patient rather than on differences in the poison [0]

Hutchinson speaks to us moderns with particular weight on this subject because he was the last of the great pre Wassermann and pre Schaudinn diagnosticians in this field He had to make his diagnoses in the same way that the medieval doctors made theirs by inspection and by the history Of the two he said history was of prime importance and yet we know how little history counted in medieval medicine and how long it took to unravel the confused story of chronic treponematous infection No wonder then that the diagnosis of syphilis was hidden so long beneath other diagnoses and carried for so many centuries under the head of leprosy

Yet there were three components of leprosy which demonstrate to us in retrospect that it comprised syphilis These as Holcomb [1] has pointed out were its contagiousness its association with sex and its hereditary feature None of these three is characteristic of true leprosy and all are eminently true of syphilis Sudhoff remarks [19] on the paradox that the concept of isolation and segregation developed in connection with leprosy yet the leprosy of Hansen s bacillus is the least easily transmitted of all chronic infections Its incubation period is reckoned in these days to be from 3 to 10 years[115] and it is not easy to assume that it has changed its nature in the intervening centuries since the Dark Age Much more likely it is that its extremely contagious character in those times was *due to its silent partner syphilis*

In the second place leprosy is in no sense a venereal disease yet in medieval times the term venereal leprosy became quite common Many causes came

of all hygienic and sanitary laws, made cutaneous disease appallingly common[110] Treatment was rudimentary and prophylaxis on an unsound basis

In connection with pilgrimage it should be noted that the Crusades (1096–1270) took hundreds of thousands to the Balkans Turkey and Syria, ancient homes of treponematosis Many came back from their journey with the stain of leprosy to help fill the leper houses with treponematosis masquerading under its name Many a returning warrior found Salerno a convenient haven for treatment on the way home[115] Some lepers' were being cured with sulfur and many more with mercury inunctions The concept of 'temporary leprosy' was growing[116]

The 'leprosy' of the physicians and barber surgeons of the Middle Ages comprised not only the acute eruptions but the gummata of skin and bones, so characteristic of the untreated 'native syphilis" of today, and the so called rhinopharyngitis mutilans the syphilis of the center of the face" of Lacapere (North Africa) and the gangosa" of yaws known in ancient Greece as elephantiasis and in Rome as mentagra

The similarity in geographical distribution has been noted there are other resemblances between leprosy and treponematosis Both are most prevalent in those countries where the sanitary and economic levels are low, and both tend to disappear as these levels rise Even more striking is a superficial clinical resemblance leading to confusion in diagnosis between true leprosy and the eruptions and mutilations of 'medieval syphilis" Even at the present time mistakes in diagnosis are made not only where the diseases exist side by side as in Africa but also in centers of medical knowledge Saunders[1 8] says 'It has been the common experience in this country that patients with leprosy have drifted from one clinic to another for years and have reached an advanced stage before the correct diagnosis was made' Yet this delay does not reflect any particular discredit upon the doctors concerned for the diagnosis of syphilis itself is perhaps the most difficult in clinical medicine Syphilologists are accustomed to having their cases 'look like something else Hutchinson[74] said 'There is scarcely a malady which has received a name which may not be simulated by it, and still fewer which it may not modify For years one of the large insurance companies has been displaying a reference to Syphilis, the Great Imitator The difficulty of diagnosis was much greater in earlier days when the cause and course of syphilis were unsure, when there were no specific tests to apply, and when there was a multiplicity of other exaggerated skin conditions and constitutional diseases to confuse, but even today a clinical teacher like Stokes[117] can still speak of its "essentially Machiavellian facility in disguise deceit and malevolence' If one lists in three columns the dermatological, neurological and mucosal conditions found in leprosy, it will be found that in the differential diagnosis syphilis stands

good and evil A common corollary equally pious but not so convincing was the statement that the remedy would be found in the place or country in which the malady first arose To question either statement was impious denial of the benevolence and omniscience of Providence and in times of religious superstition this was a serious crime

Mercury was accepted in the ancient world as fulfilling the main proposition so far as skin disease was concerned As has been noted it was used by the Chinese in the form of ointments and fumigations it was used in early times in India and was most highly developed by Arab medicine in the Near East perhaps because of the presence there of deposits of the sulfide cinnabar and because of the advance in knowledge of metallurgical processes coincident with the Moslem era

Cinnabar was the mineral used most frequently for fumigation Under the influence of heat the sulfide is broken down and the pure metal is volatilized Later the alchemists distilled off the quick silver as it was called and the liquid metal was mixed with henna or other herbs and heated in a dry vessel over a small bed of coals as may be seen among the Euphrates bedouins today The patient *crouched over the skillet as he drew his cloak over his head and inhaled the fumes* The remedy produced a copious salivation and was remarkably effective if as the Arabs said it did not make the teeth loosen and fall out Other forms of mercury were calomel and corrosive sublimate used internally and the red precipitate mercuric oxide in ointments

Rhazes about 900 introduced extensive use of mercurial ointments both among the Arabs and in the Latin West Theodoric of Bologna [4] in the 13th Century emphasized the value of unguentum saracenicum which many who had acquired leprosy in the Crusades doubtless brought back from the Near East as the *specific cure which God had provided So venereal leprosy originating* in Syria brought along the Syrian ointment and that many were cured was admitted everywhere In fact it was the treatment of syphilitics in leper houses that introduced the idea of hospitals as centers of treatment rather than refuges for the socially outcast It gradually changed them from detention camps to rehabilitation centers Salernitan physicians before 1200 used mercury and electuaries for mal franzoso were prescribed in Florentine recipe books dated *1465 but probably belonging to the period 1425–30*

It should be noted that the mercuric ointments were not designed for external application to ulcers but were rubbed into the sound skin and achieved their result by absorption For local applications the Arabs of today still use the mild medieval escharotics copper acetate verdigris vert de Grece and copper sulfate blue vitriol

Certainly much of the leprosy of the Middle Ages was related to mercury

to be assigned to 'leprosy' such as pestilential air melancholic foods, disorders of the humors but running through all the writings is a thread relating leprosy with sex Bernard de Gordon[61], the Scottish professor at Montpellier said 'leprosy' could be introduced into the uterus by a leper during intercourse or passed from one man to another through intercourse with the same woman He wrote in 1303 a description of 'venereal leprosy' conforming to the 'pustulis of Salicet who in 1275 related genital sores to constitutional disease and said pustulis came from prostitutes Gilbert Anglicus in the 13th Century was writing about leprous infection after coitus and practically every surgeon in the Middle Ages wrote that leprosy was contracted by intercourse with a menstruous woman[61]

In the third place instances multiplied wherein "leprosy" was transmitted from mother to child it was inherited Now prenatal infection with leprosy is believed not to occur[11], whereas it is characteristic of venereally acquired syphilis Variations of air and food were invoked to account for this congenital 'leprosy', but the idea persisted that here was truly transmission from mother to child So the thread runs through medical history, hereditary leprosy to hereditary morbus gallicus to hereditary lues venerea to hereditary syphilis and now prenatal syphilis[11]

It was treponematosis therefore travelling in the shadow of "leprosy", which accounted for much of the chronic mutilating infection of the Middle Ages and contributed the undertones of contagiousness, sex and inheritance Copland (1508–1547) wrote an English version of a French book of the preceding century recognizing the connection between lues venerea and an infectious venereal and hereditary disease[1] As gros mal morbus gallicus and lues venerea (the venereal plague) came into use, "leprosy" faded, not because the number of lepers actually decreased, but because diagnosis was improving The remarkable decrease in the leper population at this time was due simply to their wholesale transfer to the other disease just as the authors of the day by an equally simple process changed the names of certain chapters in their books from 'leprosy' to 'lues venerea' or 'morbus gallicus' For example John de Vigo s surgery in the edition of 1514 dropped the chapter title of leprosy and entitled the identical materia morbus gallicus[61]

Mercury

> The Prophet declares that for every malady wherewith God afflicts mankind, he has appointed a suitable remedy'
>
> (Arab saying)

This sentiment, actually much older than Mohammed, represented primitive man s attempt to comfort himself with the philosophy that life is a balance between

'The medical writings of the 13th and 14th centuries consisted of compilations commentaries and concordances the first great mass of which was based on the Latin translations of the Arabic works that were available at Toledo in Spain By this time the medical system of Europe had become a hopeless confusion of Arabic superstitions ignorance and bigotry The first medieval reports of cases were published in the 13th and 14th centuries and are in the main unintelligible [14] Until 1467 anatomy was not represented in the medical curriculum although place was given to metaphysics logic astrology and even rhetoric

Although the 13th Century furnished an Arabo Scholastic revival and was one of the great epochs of human history translation ended with it and was followed in turn by periods of mystics systematizers and transmuters but these gave way to the experimenters and now the time was ripe with promises of a great intellectual revival The Universities of Paris Bologna Oxford Montpellier Cambridge Padua and Naples were stirring with a ferment and in the century after the discovery of printing (1450) the reports of the experimenters combined with the rediscovery of the Greek originals drove the Arab culture of the Western Caliphate into a position of exaggerated contempt The publication of the fundamentally modern works of Vesalius in anatomy Paracelsus in medicine Copernicus in astronomy and Fracastoro in contagion finally vanquished the Arabist Tradition in the Latin West [14]

The concatenation of paper printing and the renascent and curiosity filled spirit of man drove scholars to extensive exploration of manuscripts maps mathematics astronomy theology and medicine It was the time when alchemy became chemistry astrology became astronomy authors began to write stories about real people artists turned from conventionalized saints and began to paint portraits and human bodies scientists forsook the authorities and planned experiments and the doctors eyes were opened to human morphology physiology pathology symptomatology and capstone of all diagnosis The 16th Century saw the general recognition of smallpox measles chickenpox influenza typhus and many other diseases That they were recognized increasingly is not to assume that they were new but that through the diffusion of printed knowledge diagnosis was improving Only leprosy faded not because fewer people were infected with Hansen s bacillus but because diagnosis was improving and its contagious hereditary venereal component was to be given a name of its own at last Beginning with the closing years of the 15th Century the literature of lues venerea morbus gallicus and mal franzoso began to grow until in 1566 no less than 58 books devoted to it had been listed already [8]

He misreads history who puts the discovery of the New World as greater in significance in the history of treponematosis than the discovery of printing It is true that as an event in history the discovery of a new continent opened men s

and history thus presents us with the paradox of a specific remedy being used extensively for a disease not yet specifically recognized and named As Garrison sums it up[43] " The end result of recent investigations is to the effect that from the 12th Century on medieval physicians were richly supplied with mercurial recipes against an anomalous group of skin affections which from their very names scabies grossa, variola grossa grosse verole, scabies mala, bose Blattern, mal franzoso, were most likely syphilitic

Sudhoff[11] says it is difficult to reject the conclusion that a cultural milieu wherein was developed the mercuric inunction treatment of a constitutional disease with cutaneous complications could not have been free from syphilis Knowledge however was unorganized unscientific and limited to the lower social strata with diagnosis and treatment in the hands of barbers When reports of morbus gallicus began to spread more widely, people recognized the description and said *that* is the disease which common people call mal franzoso In fact Hock (1514) called his book " Mentagra, vulgo mala franzoso " [5]

Paper Press and the Renaissance

" While printing and publishing did not create the Renaissance, it none the less gave impetus to it and then held its advance All over Europe the cathedral builders were reaching their triumph In Florence and Flanders, art was waking from its thousand year sleep already block printing had begun in Germany Holland and Italy and in 1450 appeared the Bible of Gutenberg, the first book printed from movable type [16] Between that date and the pregnant year of 1492 three million books had left the European presses Yet few are aware of the prior history of paper manufacture and what a fundamental role paper played in the intellectual development of mankind

Not only did the Chinese invent and perfect true paper, but from the heart of China its westward movement began It is said that the secret of its manufacture was revealed by Chinese captured by the Arabs at Samarkand after their defeat in the battle of 751 Then began the march to Baghdad, Damascus Morocco and finally, to Europe with the Moorish invasion of the Spanish peninsula in 1193 The first paper mill in Europe was established near Valencia in 1150 A D Paper spread slowly from Spain to Italy, to France and then into Germany " On the eve of the Renaissance we find Ullman Stromer outside the walls of Nuremberg establishing a paper mill and setting the paper scene for the rebirth of the spirit [16] For paper gave substance to oral tradition and became the medium through which literature philosophy and the other achievements of the human mind were made accessible to all Paper and print were the building blocks out of which the edifice of modern civilization rose

— not the slightest indication in Columbus journal of any serious illness aboard during the entire voyage Columbus actually gave thanks that he had no ill ness except in one old man with gravel He was not concealing anything his crew arrived exhausted but healthy[6]

Columbus brought back 10 Indians 4 of them from Haiti[5] One died 3 were left behind in Seville and 6 all males he took with him overland to Barcelona (He took none of his crew) The Spanish writers described the Indians as not black like Guine men but brown and comely like Easterners They observed that were these people but dressed and kept from sun and air they would be almost as white as people in Spain Columbus wrote They love their neighbor as themselves and have the softest and gentlest speech in the world[64]

Was there any treponematous infection in the New World before the Discovery? Hamlin believes so and says yaws was undoubtedly indigenous in remote parts of South America as well as in Africa Australia and Melanesia for centuries before any contact with European races was established Scott[1] says It would appear that when tropical medical history began pian frambesia yaws existed in many regions of the world as far apart as the east is from the west Hamlin[3] would have the infection accompany the human migration from Asia and reach the New World over the Alaskan bridge Holcomb s study of syphilitic skulls in the Aleutians[6] gives support to this possibility Morison[4] says We may consider it proved that syphilis in a mild form existed among the American Indians before the coming of the White Man but he does not cite the proof Scott[11] says The fact — it appears to be factual — that the disease was present in the west before Columbus day concerns of course the question of its primary introduction only On the basis of certain skulls Williams[1] concludes that syphilis arose in the New World in the past 10 000 years but Hrdlicka says that no incontestible pre Columbian syphilitic bones have been found in the Western Hemisphere

It is possible to assume that treponematosis had reached the New World without at the same time assuming that the Amerinds of Hispaniola had it but if they did the disease would certainly have been of the juvenile type so familiar among primitive peoples including the present inhabitants of rural Haiti Columbus and his chroniclers in that case should have remarked in their copious note the prevalence of huge skin ulcers swellings of the bones and the horrible disfigurement of gangosa Details of the natives are given in all respects but no mention is made of any such conditions

If the 10 Indians whom Columbus took back with him had ever had treponematosis they had recovered long since from the childhood infection and were no longer infectious to others If they had had the mucocutaneous lesions of relapse they would not have been selected for Columbus the showman would

minds and fired their imaginations The obsession of Islam which had dominated Spain s history for seven centuries was, in a way, characteristic of the whole of Europe The acme of European enterprise outside Europe had been reached in the Crusades — South Eastwards, neither East nor South, nor least of all West, blocked as it was by a veil of nothingness Of recent date the Portuguese had won the admiration of all Christendom by their navigating exploits along the coasts of Africa and as far as the Isles of Cabo Verde But the veil still remained hanging over the ocean and Christendom had never imagined anything outside its own pale but Moors and Jews and the somewhat mythical and fabulous subjects of Prester John or of the Grand Kahn " [4]

This was all true and then came the sudden expansion of geography and the heady wine of discovery No wonder that the drama of the event shed a blinding light over all contemporaneous history It is only a pity that medical historians at various subsequent periods have been so obsessed with the significance of the Great Event that they have lost their historical perspective Sheer post hoc reasoning is the only basis for attributing to Columbus the introduction of syphilis into Europe For two great stimuli focussed simultaneously upon the intellectual life of Europe One of them represented by the art of printing, the production of cheap books the easy exchange of ideas, clinical experimentation, observation and report, brought treponematosis into the light and gave it a name The other the return of Columbus with his 44 sailors and 10 Indians, affec ed the history of treponematosis not a whit Blot out the return of these 55 men the march of events as regards syphilis in Europe remains as it was, a consistent historical whole

Christopher Columbus

> " Let us not say it was brought from America by Indians and thus expose our simplicity by so doing
>
> Blondus (1497–1565)

Columbus returning from the New World reached Lisbon March 4, 1493 with a crew of 44 and 10 Indians [7] Evidence of syphilis among his sailors is wholly negative and so emphatic a negative as to throw strong doubt on the possibility of their having brought the disease to Spain[94] As Morison says There was a period of 22 weeks from the first possibility of infection at San Salvador, and of about ten weeks from the last possibility of infection at Monte Cristi to the end of the voyage (i e between October, 1492 and January 1493) By mid November at the latest every Spaniard who had become infected in the Bahamas would have been on the sick list, and on the homeward passage Nina and Pinta would have been short handed to the point of danger Yet there was no sick list

mercury, the specific for leprosy [45] Senareze said the disease antedated Charles VIII Villalobos (1498) described induration of the primary sore and thought the disease new in Europe but treated it with mercury and did not ascribe it to the returned explorers[45] He and others spoke of an epidemic of bubas in Baeza in 1488 Torella [5] said the new disease was in France in 1493 and went from there to Spain and Italy He called it pudendagra stressed contact as the cause and reported how children got it from wet nurses He recognized the infectiousness of the chancre described primary and secondary stages and gave symptoms of the eruptive stage involving skin and glands He used mercury and advocated prophylaxis Brunschwig spoke of morbus gallicus on the Rhine in 1493, and Nibling described it in Heidelberg in the nineties[119] Morison finds it significant that Barcelona is near France facilitating the hypothetical transmission northwards but Scillacio writing to a fellow physician from the spot said the disease had come to Barcelona from France in 1495

Oviedo *the official historian of the Indies and one of the authorities most* widely quoted by the theorists was a page at the Court in Barcelona when Columbus arrived but makes no mention of having seen or heard of any epidemic of new and strange disease Writing 30 years later he says bubas was brought from the New World but did not appear in Spain until 1496 after the second voyage In fact Morison who puts so much credence in him admits that Oviedo falsified the record in an impossible story about Spanish ships bringing the disease to Naples Yet bubas is an old Spanish name Ruiz de Isla said it was used as a curse word 10 years before the Discovery and Montejo says the word was in the Spanish literature before 1492 In the Dance of Death 50 years before Death calls a victim to die of buvas [7]

Ulsenius ascribed to the new disease an astrologic origin with the date of 1484 Hock gave the date 1483–7 and Steber of Vienna 1484 There are possible references to it in Mainz records in 147 and a pestilence in Denmark in 1483 Many wild explanations for the appearance of morbus gallicus were offered during the closing years of the 15th Century Some said it came through eating of human flesh in Naples from intercourse of a woman in Valencia with a leprous knight that the Spanish poisoned the wells in Naples and put plaster in the bread of the French that the French in Naples drank wine contaminated with blood of lepers by retreating Spaniards These are the contemporary stories In only one instance is Columbus mentioned and that is a story that he brought the disease from Calicut to Naples in 1496[1] This fable reported by Montanus (about 1550) had Charles VIII ' besieging Naples long after he had left Italy [8] The most sensible statements were made by Fracastoro in 1546 and by Blondus (1497–1565) who is quoted at the head of this section Fracastoro said he could not see how a few sailors returning from the Isles of Spain could have spread a

wish perfect specimens for the appearance at the Spanish Court Morison[4] says they "reasonably carried spirochetes in their blood streams (sic) and passed it on in the usual manner" but an elementary knowledge of treponemal infection precludes the possibility of spirochetes in the blood and transmission from such cases through intercourse If they had been women, there might possibly have been lurking relapse lesions in the vagina, but these were all men It is inconceivable that these 6 strangers, introduced like gold fish in a bowl to the curiosity filled Spanish Court, could have had infectious spirochetal lesions so occult that they were not remarked upon and yet so contagious as to permit Morison to hypothecate " and that leaves over a year for the disease to cross the Pyrenees to Southern France, before the army of Charles VIII got going "

As a matter of fact the treponeme did not have a year, for in the very month (March 1493) of Columbus arrival in Lisbon an ordinance was being issued in Paris against la grosse verole[11] Some writers, admitting the absurdity of attributing to these 6 men the introduction of treponematosis into Europe, have fallen back upon the assumption that subsequent landings of Amerinds and returning Spaniards brought the infection but chronology thoroughly disposes of this theory for by that time morbus gallicus was already being talked and written about in every city of Europe For the advocates of the American origin of syphilis it is a case of "first voyage or none" This fact is of prime significance Furthermore if treponematosis was being brought over by the boat load, it should have been recognized at the dock side or at any rate in each port in turn to which the caravels returned For a hundred years the ports of the Mediterranean countries had been alerted to the introduction of disease by ship The Black Death, which arose in the 14th Century, led Venice and Marseilles to pioneer in the sanitary control of vessels from the East with observation stations for detention, isolation and even disinfection The first quarantine station in Marseilles was established in 1383[11] and yet the "theorists" would have this new disease, described by them as frightfully contagious, escape from ship after ship undetected burrow its way unseen through Spain cross the Pyrenees and turn up fresh in Charles army Morison says the first reference to los bubas in Seville concerned prostitutes in 1497[4] Oviedo distinctly says bubas did not appear in Spain until 1496

Yet neither Columbus nor any of his fellow chroniclers, some of whom were physicians nor any contemporary Spanish authority literary, medical, religious or civil mentioned the existence of disease on the ships or attributed the importation of any disease to Columbus or his fellow travellers In fact, contemporary opinion concerning morbus gallicus all pointed another way Delicado[6] said the disease was in Europe in 1488 Widman (1497) recognized acquisition of the disease from prostitutes and drew the analogy with venereal leprosy He used

Within a few decades the stories of great contagion fatal symptoms and extreme epidemicity had faded and treponematosis had settled down to be treponematosis again Ah, say the theorists but this was a new disease and being new it hit Europe harder Yet how could treponematosis be so new to Europe when streams of infection had been pouring into it from Africa since paleolithic times? Furthermore it is gratuitous assumption to argue that this is the way syphilis would behave if it were introduced into virgin soil Treponematosis has two epidemiological patterns and a transitional phase Practically speaking contagion in all phases is by body contact a fact which is due to the biology of the parasite The juvenile nonvenereal pattern is more contagious than the adult venereal type for obvious reasons The transitional phase which combines epidemiological features of both patterns also far exceeds the venereal in its spread for it includes many opportunities for extragenital and juvenile infection The medieval treponematosis of Europe comprised all of these epidemiological patterns writers in the early days did not stress sexual contact often seemed to know nothing of primary lesions a fact which signifies the presence of a large transitional component *Compared to modern European syphilis the disease of 1500* would naturally be regarded as more contagious and more spectacular and it is not necessary to assume that for those few decades the treponeme suddenly changed its habit of personal transmission became blown about by the wind or persisted on clothing or was carried by some insect vector Yet one or other of these devices would be necessary to fulfill the hypothesis of sweeping epidemic unless one were willing to suppose that the parasite underwent mutation to something quite different for two or three decades and then as suddenly resumed its former character

A balanced and moderate presentation of the orthodox view of the epidemic is given by Singer [4] During the Middle Ages there had smouldered in various districts an obscure di ease sometimes more or less dimly distinguished under various specific names but most frequently confused with leprosy Toward the end of the 15th Century this disease which was still imperfectly distinguished in men s minds from leprosy broke out in epidemic and virulent form all over Europe It caused great destruction of life and developed everywhere as a problem of national importance *Various titles were given to it such as* pox *the French* disease the Spanish disorder Only tardily was it recognized that the disease usually *was of venereal origin* Not until 1530 *on the suggestion of Fracastoro* did it receive its modern cognomen of syphilis

That as has been said is the conservative view of the epidemic For the richest elaboration of the theory however one must read Bloch and Pusey The latter says syphilis in Europe is a story without prologue Syphilis is the one disease whose history begins with a definite date That date is the date of the

disease so widely in so short a time, a disease which appeared simultaneously in so many countries of Europe

Like King Charles' head which always kept coming into Mr Dick s Memorial King Charles VIII always keeps coming into the story of the e times He left France September 1 1494 with an army of 20 000 to 30 000 men drawn from France, Germany, Switzerland, Portugal and perhaps, Spain[15], although Morison doubts the Spanish contingent [4] These were the usual mercenary troops, and there were the usual hangers on including many women Of the lowest class these men and women must have brought with them from all over Europe a heavy freight of all known infectious diseases including treponematosis in the form of lues venerea or venereal leprosy Charles reached Naples in February and entered the city unopposed There was no siege of Naples ' as alleged by some He left Naples in May of 1495 with 9 000 men and travelled north but his army was not yet out of Italy when on August 7 the Emperor Maximilian issued an edict at Worms which showed that the disease under several names was already well known in Germany[4] The Edict calls the disease bosen Blattern, the evil pox, morbum franciscum It is true that the reference is to " a new and never before seen or heard of disease , but the multitude of current synonyms invalidates this sweeping statement Contemporary names at the time of Charles were pustulis, asaphati leprosy mentagra, elephantiasis malum mortum formica morphea essere pruna bubas the diseases of St Job, St Lazarus St Menus, St Minus St Mitis and many others[4]

Holcomb[5] and Madariaga [4] have called attention to a contemporary event which may have had a bearing on the story of the time While Columbus was making final p eparations for his departure from Palos in 1492 the expulsion of the Jews from Spain was ordained and hundreds of thousands left Spain on the very day Columbus chose to embark (August 2 1492) Many died at the hands of pirates and Saracens but it is estimated that 160 000 lived to be scattered throughout Portugal Germany England France Italy and North Africa No less than nine shiploads arrived in Naples in August 1492 Now large bodies of refugees of this sort in those days as even today must have been disseminators of disease, chief among which would be louse borne typhus and possibly also typhoid, diseases which at that time were not differentiated Sudhoff[119] believes that there was an epidemic of typhus in Naples under the prevailing inexact notions of diag nosis such an epidemic could reasonably be confused with any new disease

The picture presented by the theorists and surprisingly accepted as the orthodox view by most historians, is that morbus gallicus while the name syphilis was still 50 years away in the future under a variety of local names spread over Europe within a few years with extren e rapidity great contagion and very acute and fatal symptoms But this is unlike any treponematosis before or since

intercourse, as there are in some African communities which have felt the touch of civilization but there were also eruptions and fevers ulcers and mutilations depigmentations and swollen bones such as are presently seen in juvenile treponematosis in *Haiti, Polynesia and Syria*

However as the early decades of the 16th Century passed the fevers the exhausting and prolonged illnesses the deaths came to be recognized as due to other diseases such as pneumonia tuberculosis meningitis smallpox leprosy *typhus and typhoid any of which might have occurred coincidentally with syphi*lis So the spurious epidemic passed and syphilis became milder Fracastoro notes a change from florid skin eruptions to a picture of venereal lesions and late ulcers Actually the treponematosis that was to be called syphilis had not become milder but diagnosis had become more accurate Further, treponematosis in Europe, as sanitation improved was passing out of the nonvenereal into the transitional phase and more and more cases of frankly venereal syphilis were being seen Treponematosis was endemic not pandemic in Europe and it never became epidemic The endemic prang from the pool of venereal l prosy al readv in I urope augmented by contributions from the Near East at the time of the Crusades and by the black slaves that had been brought for centuries from Africa

About 1500 there is a sudden interest in a new disease a kind of panic runs through Europe defensive measures are taken it is out of style to have leprosy morbus gallicus is the mode of the times all kinds of wrong diagnoses are made many deaths are ascribed to the new disease but in the course of three decades the shape of syphilis takes form diagnosis becomes firmer at last it is realized that this is the old venereal leprosy which mercury cures and the epidemic is over[11]

Here is the explanation of the epidemic which did not take place It is too rational an explanation for those who like Pusey and Bloch prefer drama to biological verisimilitude but it is consistent with the nature of the treponeme the psychology of man and the environmental conditions of medieval Europe Castiglioni [9] says syphilis was brought slowly into the group of infectious diseases without its ever having assumed the same pandemic dimensions as leprosy and *plague and he believes this is due to energetic treatment and wide diffusion of* knowledge This may be granted but when he says that it did not become epidemic was the crucial test of the new medicine he gives undue credit to medicine and neglects the fact that by its very nature syphilis could not become epidemic In any case it was not many years before the pseudo epidemic was over for the same writer says by 1520 any intelligent physician was in possession of current knowledge about the disease the danger of contagion and its various manifestations and the treatment to be recommended

discovery of America It appears on the stage of history with a dramatic suddenness in keeping with the tragic reputation it has made, as a great plague sweeping within a few years over the known world " Bloch[1] declares there is not a particle of evidence to show that the disease existed in Europe before the years 1493–1500 In the entire literature of the Old World, both occidental and oriental no description of the syphilitic syndrome anterior to 1495 is to be met with He refers to the great epidemic " in these terms, ' Its sudden mysterious appearance and its unknown nature caused the disease to make a profound impression everywhere and to strike all men with horror It was the syphilis of Haiti which was the unhappy source from which the poison was shortly to stream throughout Europe and the Old World "

Both these writers refer to the ' sweeping epidemic " of syphilis, as do others to this day, as if it were a historical fact instead of a theory to fit a set of facts In order to accept this theory one has to forsake for the moment all one knows and believes about the epidemiology of treponematosis The treponeme is a fragile parasite an obligate of man, transmitted by one person to another in a chain of individuals

Even Zinsser[134] surprisingly was willing to postulate a change in the spirochete to account for its supposed sudden change in behavior But this is like the device of the old Greek tragedians, the deus ex machina, who stepped out of the wings and set things right when the tragedy got tangled beyond all human solution Fortunately for those who abhor ' freak explanations of natural phenomena, and who prefer to find the golden thread of consistency in biological behavior, there is a sounder explanation for the facts

This has been offered by Sudhoff[119], Holcomb[57] and others in the following terms Treponematosis about 1500 was emerging from a confused medley of skin diseases and chronic constitutional infections, chief among which was ' leprosy " As morbus gallicus and all the other names began to be applied to it by the people in those times, many current fevers and skin diseases were attributed to it, diagnosis being what it was

The common people had begun to recognize the treponematosis which was among them and whole blocks of leprosy patients were suddenly said to have the great pocks or mal franzoso So the pendulum swung to the other extreme, as it does in human psychology and many extraneous conditions were included with the disease, for if there was a ' new disease ' around, all otherwise undiagnosed conditions would certainly be attributed to it The terrible conditions of sanitation and hygiene in Europe have been noted, and doubtless much of the syphilis was of the nonvenereal type conveyed from one member of the family to another by extragenital contact as among the Arab and Russian villagers in many places today There was a venereal element attested by chancre after

great quantities under the mistaken notion that it was a specific for morbus gallicus Apparently used by the natives as a purgative its medicinal virtues were built up by a clever sales campaign which brought in great profits for it was a crown monopoly This was lignum vitae or guaiac a particularly hard and heavy wood, which was promptly endorsed by most contemporary writers, including de Isla and Fracastoro who however in other portions of their books clung to mercury as the best remedy There were some independent spirits among them Blondus (1542) who said the wood made his patients bloodless ghosts and he did not regard it highly As in many rackets before and since this one had a strong religious flavor The old Arab doctrine was revived every disease has a remedy provided by Divine Providence in the country of its origin Therefore bubas came from the West Indies and if bubas came from the West Indies therefore the wood must be God s gift to suffering man Thus each hypothetical statement became the premise for the other Cases of bubas seemed to improve after consuming copious infusions of the wood To the devout bubas or morbus gallicus must have come from the New World for the remedy came from there and to deny this was to deny the goodness of God Thus the sale of the Holy Wood as it came to be called was stimulated and the revenues of Spain swelled There was also undoubtedly the feeling among the devout and the pseudo devout that it would be convenient for Christianity to hand over the origin of this disease to the American Indian thus relieving the Christian nations at a single stroke of all responsibility for this supposed disgrace and chagrin [5]

Thus there was a strong commercial interest with considerable religious bias behind the original concept of American origin The church and state in Spain were bound closely together not least in their finances The church was extremely powerful in all walks of life and in the new field of printing was supreme Through its assumption of censorship it could withhold or permit publication and since Oviedo and Las Casas trimmed their writings to this fact their witness on the subject of the American origin has no place in a critical study

Ruiz Diaz de Isla unlike them was a physician He lived in Spain and never travelled abroad His book bears license date of 1537 and publication date of 1539 and he says he completed his classification in 1530 [7] Therefore it was printed and probably written after Oviedo and probably was influenced by that writer In his manuscript he calls the disease the malady of the Island Hispaniola the disease commonly called bubas but in the printed book it is called the Serpentine disease These two names have interesting connotations for bubas buvas or boas antedated the Discovery by many years and Albucasis in Cordova over 500 years before had described four kinds of leprosy one of which was the serpentine disease De Isla was too good a doctor to describe the disease under a new name but he was a circumspect Catholic and with an eye

Ruy de Isla, Fracastoro and the Holy Wood

Three authors of the early 16th Century are cited by Bloch[1], Pusey[103] and more recently by Morison[94] as chiefly responsible for first advancing the theory of American origin These are Oviedo, Las Casas and Ruy de Isla (1462–1535) Oviedo, courtier and scholar, friend of Columbus son, was in Italy and later in Haiti and Central America His Summaria was published in 1526 and his Historia in 1535[5] Writing 30 years after the event he said the natives of Haiti had bubas and it was brought to Europe by Columbus and his men, but he said this happened on Columbus' second return and that Gonsalvo de Cordova carried it to Naples by sea Morison points out that this fleet gathered in 1495, the year before the second return, and reached Reggio on May 26, a week after Charles had started north, so that this part of Oviedo s story is 'definitely false' [94]

Las Casas wrote even later (1550) He went to Haiti in 1498 at the age of 24 Pusey quotes him as follows, 'I took the trouble on several occasions to interrogate the Indians of this Island as to whether this disease was of great antiquity, and they answered yes" Now, can anyone with experience of interrogation of primitive people put one jot of scientific value upon such a question and such a response? The primitive man answers in the fashion which he thinks will be most pleasing to the dominant white One can say about such a leading question that it is impossible to know whether those who answered were lying or telling the truth, selecting the most pleasing answer or just failing to understand Yet Pusey cites Las Casas as the final link in the proof of American origin[103]

Las Casas says the disease was imported to Spain by Indians or Spaniards and later was called the French disease because of its association with the army of Charles VIII Oviedo says Columbus men contracted the disease from Indian women and brought it to Spain He says it should be called the West Indian disease rather than the French or Neapolitan disease Here is a noteworthy point Treponematosis is a disease of many names It is often called by an indigenous name, but of all diseases it has been most prone to the sobriquet, the "foreign" disease Here of all times was the time to call it so if the dramatic story of Oviedo and the rest is to be believed But no in Europe it was always bubas, 'leprosy ", morbus gallicus, the great pox and never the West Indian disease or the imported disease The doctors and the people of Europe with the perspicacity of the common man were not to be deceived with travellers' tales about a romantic origin

These two witnesses were writing 30 and 50 years after the event Had they any motive conscious or subconscious for distortion of facts and misrepresentation of events? Undoubtedly they had for on Porto Rico, which was explored in 1508[57], a wood had been found which soon came to be imported to Spain in

These two stages are acceptable and thoroughly consonant with present knowledge of treponematosis De Isla s third stage however must be repudiated as having nothing to do with syphilis

The first stage he said consisted of an eruption without pain itch or matter and without ulceration It disappeared within a year and 98 per cent recovered entirely with spontaneous healing In this stage tumors appeared on the vulva and in the groins sometimes preceding the general eruption by about 2 months There was also dysphagia The disease was acquired he said by conversation i e by contact and he advised regarding precautions saying that washing was the secret He advocated inspection of public women and isolation during the infective period He admitted that religious persons virgins and children honest and respectable people were affected also but attributed this to innocent contacts [7]

The second stage corresponding to late syphilis came on within o years at varying times with pain pustules and ulcers Although the first stage was very contagious this one was not — sage observation In fact he said intercourse ithout infection is possible once the first tage is over Now there was pain in the bones at night and ulcers in the throat soft palate uvula and nares The dis ease was one of crusts and scabs rotting of bone collap e of nasal bridge clavus and fissures in the soles loss of teeth perforation of the palate loss of nose and eyes hoarseness and loss of peech ulcers of scrotum and vulva sequestra and running sores from the bones of the arms and legs This is a remarkably faithful picture of untreated late treponemato is just as described by Lacapere in North Africa [9] Chambers in Jamaica and von Duhring in Turkey [5]

If de Isla had stopped at this point his standing as a clinician would have been unimpeachable and his description of medieval syphilis a clas ic But he was a child of his age and we with the superior wisdom of hindsight must part com pany with him at this point For he goes on to describe a third stage which has no part or parcel in treponematosis This consists of a continued fever lasting from mid afternoon to sometime after midnight followed by sweat and accom panied by thirst loss of appetite emaciation and pallor The legs and feet swell there is diarrhea with incontinence colic and finally horrible excessive stools The abdomen swells with persistent tympanites the face is jaundiced or icteroid the breath is putrid and the lips and tongue covered with sordes and surrounded with flies [7] many patients die There was no mortality in the first and second stages only pain and inconvenience and mutilation but now comes death Is there a medical student who would not be reminded of typhoid carried by those flies from those copious stools in an epidemic or of typhus carried by the ever p esent louse? In any case here we see through one doctor s eyes the great epi demic of syphilis which swept over Europe Syphilis was there all right just

to the powerful religious and civil sponsors of the Holy Wood he accepted the American origin in his title He did not gainsay the efficacy of the wood but he gave the disease an old name and said the best treatment was with mercury Three things heal, he said, diet, sweat and salvation (by mercury) of there the last is most important He identified bubas with the serpentine disease of the Arabs and with mentagra of the Romans and used other good medieval words such as lichens and empeines as if he were unaware of the discrepancy While satisfying the pious he added that the wise would be able to distinguish the truth

De Isla as a clinician is entitled to respect De Isla says he treated some 20 000 patients with bubas some for as much as 20 to 40 years He may have to be forgiven some exaggeration but he had full right to speak for the current conceptions of bubas He practiced in the places where bubas was most to be found, the big port cities of Barcelona and Lisbon and in Seville fed by the port of Cadiz Then as now treponematous infection and venereal disease flourished in conjunction with shipping The spirochetes of yaws had been coming into Lisbon from West Africa for over a hundred years All the treponemes of the Mediterranean had been going in and out of Barcelona for hundreds of years Seville had a large population related to slaves bringing similar infection from North Africa Much is made of the statement that de Isla was in Barcelona soon after Columbus return and that he treated a Pinzon[1] It is difficult to read any significance into either statement

As a venereologist de Isla went to the big ports where the most people had bubas, and if Pinzon which was a common name is meant to refer to one of the brothers who accompanied Columbus it must be recalled that the Pinzons were from Palos and the Paleños were old rivals of Lisbon in the slave trade,

" sailing to the Canary Madeira and Cabo Verde Islands, and trading with the coast of Guinea and the 'Mine' in all kinds of commerce including black slavery for which they often contended with the Portuguese in the 14th and 15th centuries "[84] The Pinzon brothers were old hands on the West African coast and, if one of them was treated for bubas by de Isla, — of this not only is there no proof but Holcomb [7] has produced convincing negative evidence — it would be more reasonable to assume that it came from some of his youthful journeys to the Slave Coast

De Isla said the disease had three stages This immediately suggests the subdivision of syphilis into primary, secondary and tertiary which Ricord first established in the 19th Century [0], but these stages are not consistent with those of de Isla His first stage comprised what is now meant by early syphilis, i e from the inception of the disease to the disappearance of secondary lesions His second stage corresponds to tertiary syphilis or what preferably is called late syphilis

> 'I consecrate my rhymes
> To this unbidden guest of twenty climes
> Although unwelcomed and eternally

Book I is devoted to enumeration of the various current theories of origin such as astrologic conjunctions contagion from animals or from winds and to a description of the disease He speaks of various planets which have met and of goats fish and birds being infected Of the contagion he says Its form and seed will vary everywhere

> The wanderers that in the woods remain
> Bear the contag on far and wide and yield
> To man who is a very fruitful field
> The passion that battens on him and to his bane
> So clotting blood attests in rotting vein
> Creeping along too sluggish and too fat
> When for the virus man s a blood thickened vat,
> In fearful mysteries there poisons blent
> To bring to man adulterous ferment

> ' *Dying by inches as his soul sinks he*
> Finds on his limbs a hideous leprosy
> Upon his very bones would caries fling
> Its banners till they open to the eyes
> His lovely eyes that were so long alight —
> *Ulcers devour these — a hideous sight*
> Purulent poison too his nose corrodes
> Until for vicious humors it explodes

This is de Isla s second stage the late lesions of syphilis syphilis of the center of the face and the gangosa of yaws

Fracastoro starts his second Book with encomiums for his religious patron Cardinal Bembo and he passes on to further adulation of the Pope Leo X Then he comes to a discussion of the treatment of morbus gallicus Shun south wind and rain he says and fly from marshes and damp places Seek mountains and sunshine fresh air Exercise much in hunting and gardening encourage sweating and avoid anxiety refrain from sexual activity And now follows a long list of remedies herbal and mineral with praise for each and directions how they shall be prepared as infusions or ointments combined with oil and honey Copper nitrate and other caustics are described as well as the salts of lead antimony and mercury above all mercury As a fact he said elsewhere the action of mercury on the scourge is marvellous [15]

as de Isla described it in his first two stages but it didn t " sweep ' and it didn t kill That was the work of something else, represented by the third stage , a disease that travelled through the air or the water or was carried by flies or lice a disease with entirely unsyphilis like epidemiological properties[57]

Because de Isla was misled into including so much in his description, he was forced into an insoluble dilemma for at one time he acknowledged that transmission of his disease was by person to person conversation or contact and at another described it as spreading like wildfire through the community Morison[64] says he is not impressed by Holcomb s attempts to discredit (sic) Ruiz de Isla by pointing out his inconsistencies ' Modern hyper criticism ' he says, " can similarly discredit any 16th Century tract " Holcomb, however, has not discredited de Isla By proper interpretation of de Isla he has discredited the hypothesis which Morison defends and that is a very different thing De Isla shows 1) the inconsistency of a man who wishes to describe the disease as he sees it, but knows that he will never get permission to publish unless he pays tribute to a commonly accepted — and religious — dogma concerning its origin in the Indies and its specific cure with the Holy Wood, and 2) the inconsistency of an over enthusiastic diagnostician who, in a lifetime of experience, has formulated the picture of a disease and has been persuaded to bring too much within the frame features which are epidemiologically incompatible

The fact is that as Morison himself says, the dogma of the Holy Wood was erected by a process of first reasoning backward to prove the origin of the di ease and then reasoning forward to enhance the value and push the sale of the wood Oviedo as Morison points out, says nothing of bubas and lignum sanctum before the appearance of Fracastoro's poem but afterward links Columbus and the New World with both De Isla followed Oviedo in point of time Morison finds it suspicious but not necessarily conclusive, that no one located treponematosis in America until after the guaiacum ' cure " was found, 20 years after the Discovery

Fracastoro wrote his book in 1521, and it was published in Verona in 1530 It was called Syphilis sive Morbus Gallicus and was dedicated to Cardinal Bembo[4] Whether Fracastoro intended to give the fanciful name Syphilis to the disease long known as Morbus Gallicus is not clear Certainly it did not come to be called syphilis immediately It was not until 1717 that Daniel Turner first popularized the name in English medical literature, before that it was morbus gallicus and lues venerea Castiglioni says it was not until about 1850 that the term syphilis began to replace in general use other synonyms such as lues venerea "

Fracastoro was no provincial that his view of this disease was far from parochial is shown by his first lines,

another treatise said he saw many made worse by guaiac and brought beyond cure [7] but inconsistency had no terror for him for this was poetry and the imagery of folk lore So he begins with praise of the intrepid sailors of Columbus who wandering in the magic forest kill some sacred birds and are cursed by one of them Then idealized beings representing the native inhabitants appear and proceed with games and feasting until some begin to erect altars wave the Holy Wood over the sick and prepare a sacrifice Then to the inquiring sailors they tell the story of Syphilus the unfortunate shepherd who worshipped Alcithous the king in place of the Sun God and was cursed for his blasphemy with a disease of ulcers and body pains but a heavenly creature dryad this time showed them the holy tree from which the leaves and wood were used to cure Thereupon the Spaniards sought their vessels that same day fearing the scourge

> The Sailors hit
> By this dread malady will die of it
> Or what is worse infect full many a city
> Implore the ancient forest to have pity
> Also the lignum sanctum stem you must
> Cull lest disaster fall on everyone
> For a bird murder and an outraged sun
>
> ' Destiny chooses you O Spain sublime
> To bring this treasure of a distant Clime
>
> ' Now lend your fame to this old universe
> Mingle your name O Bembo with my verse
> That lignum sanctum s marvels may be shown
> And that my vigil s findings may be known

So the shadow of the Holy Wood wrapped in the poetic fantasy of Fracastoro casts a cloud on the testimony of Oviedo the inaccurate historian Las Casas the credulous interrogator of the natives and de Isla the conscientious physician embarrassed by a medico theological racket What support remains for Morison s bold statement Thus we have three separate independent and reliable authorities writing between 1535 and 1552 as to the American origin of syphilis Las Casas Oviedo and Diaz de Isla [8] ?

As a matter of fact there is nothing in the whole story incompatible with the interpretation that the first Spaniards took bubas with them to Hispaniola for when Columbus returned to the island in 1496–7 he found of those he left there no less than three hundred Christians had died of various complaints not only as Oviedo says because the food and bread of Spain is of a tougher digestion

"All men concede that mercury s the best
Of agents that will cure a tainted breast
To heat and cold sensitive s mercury
Absorbing the fires of this vile leprosy
And all the body s flames by its sheer weight,
Dissolving humors th it it recreate
The health and with a fine, divided art
Applied to quench the flames right to its heart
And delving deep to every injured part

'Pause for a moment Muse, suspend your course
And tell what hand divine will show the source
Where all this precious, hidden metal lies
And, for this boon then let me thank the skies"

In answer to his own rhetorical demand Fracastoro then tells the mythical story of the origin of the use of mercury It happened in 'some fair Syrian valley" (note the Near Eastern locale), where a man named Ilseus, stricken with the disease is pitied by a nymph who leads him to a spring in a bleak abyss with a sulphurous wave ' and quicksilver mixed and hardened and left to cool (cinnabar the mercuric sulfide of the Arabs) Your body you must lave within the river s bright metallic wave — heroic remedy", she says "That s quick silver flowing swift Lave yourself thrice within its metal pool" The mercury changed his body suddenly to complete health and he ran off praising the Gods

"And unto twenty folk was soon revealed
Mercury s fame and what it had concealed
Of power, this liquid metal
Rub yourself well but with a hand discreet
Avoiding head and heart, right to the feet"

"Within your mouth ulcers you'll see anew,
But these will disappear and quickly too"

Having thus established mercury soundly as the specific cure of morbus gallicus and dismissed the complication of stomatitis Fracastoro in Book III abandons himself to poetical extravaganza in a flight of fancy connecting his subject with the New World and the Holy Wood It would not do for him to ignore the superstitions which were going the rounds about the marvellous efficacy of lignum sanctum vouchsafed to man in the Indies and adduced as evidence to the credulous that it was there that the disease first appeared Fracastoro in

of the 15th Century and Rosenbaum (1807–1874) first suggested that the epidemic in Naples was typhoid Virchow (1821–1902) concluded syphilis must have come from America because no one had ever found a pre-columbian syphilitic bone in Europe but Lancereaux was finding unmistakably syphilitic skulls in leper cemeteries in Paris where one might expect such to be found Parrot (1877) in the meantime was reporting prehistoric syphilitic bones in Peru but no one had ever found syphilitic bones in the West Indies the reputed home of syphilis

Buret (1890) said syphilis was universal and ancient and had been traded from continent to continent He anticipated the time when no one would believe the story of the American origin of the disease Rat[1 5] in 1891 said If syphilis did not originate in Europe there is far greater probability of its having been brought there by the Moors who settled in Spain seeing that yaws and syphilis had both existed in Africa long before the discovery of America Around 1900 Unna favored and Prokosch repudiated the American origin A decade or two later Bloch and Lusey were for it and Sudhoff and Garrison against it Holcomb[7] recently has made a solid contribution to historical research on the subject and describes the American origin as a myth Yet about the same time (1938) an otherwise excellent book on syphilis[96] has this to say in its introduction In 1493 da Isla a physician of Barcelona treated the pilot and several members of the crew of Columbus ships for a new disease supposed to have been contracted from the women of the West Indies The prostitutes along the Barcelonian water front soon had it They generously passed it along The loose morals of the day did the rest the disease became epidemic And Moore in 1945 says it has seemed profitable to review the chemotherapy of syphilis over a period of 451 years from the first appearance of the disease in Europe in 1493 until the present day Even Morison whose discussion contributes so much to proper orientation of the subject is unwilling at the end to stand by his own evidence and falls back on anonymous authority The pressure of orthodox opinion is too strong for him Although he admits that Columbus men probably were not responsible he says In the opinion of most authorities whom I have consulted the virulent outbreaks of syphilis in Italy in 1494–1496 point to an outside source of infection The hypothesis that it was introduced by Columbus Indian captives is plausible and supported by three reputable writers of the middle of the 16th Century So the preponderance of evidence seems to point to America as the original home of the Sinister Shepherd * It is regrettable that a non medical historian should have been led by deference to his medical confreres into such post hoc reasoning and that the authorities upon whose opinion he based his conclusion should now in turn be able to quote him in support of that opinion

The time which Buret anticipated has not yet arrived but there are some

and the air of Spain was thinner and colder, but because the amorous Spaniards contracted a terrible disease in the arms of the Indian women, which they called bubas[84] Doubtless the mortality was due to dysentery and malaria (references to food and air suggest this) That the treponeme was there also can be freely granted, and that it should be blamed by the Spaniards on their native partners would be most natural Perhaps some of them did acquire their bubas via the women, but the crux of the question is who introduced the treponeme into the mixed community and as to this suspicion falls on the Spaniards If the women had treponematosis, it would be of the juvenile type, and they would be relatively non infectious, or their florid mucocutaneous eruptions would be repulsive even to the " amorous Spaniards " It looks more like an outbreak of venereal syphilis in a group of promiscuous non immune men and women initiated by someone with a chancre or mucous patches The tone of bland self exculpation employed by the Spaniards is reminiscent of tales told in the venereal disease clinic Syphilol ogists are notoriously skeptical of the accuracy of their patients' 'histories ' Of all people they ought to resent such romantic hyperboles as ' it seems as if the sinister microbe had found a new virulence on discovering what, for it was the new continent of the white race " [84]

The Subsequent Course of the Theory of American Origin

To judge from the assurance of some modern writers the American origin of syphilis in Europe was established firmly within the first 50 years after Columbus and never has been seriously challenged since but such is by no means the case The theory has waxed and waned several times in the intervening centuries With the exposure of the spurious claims of the Holy Wood the corollary of American origin fell into contempt Madons (1615) proposed three possible theories 1) venereal excesses 2) the New World and 3) multiple discharges (fermenta tion?) in the vagina of one woman In 1640 the theory was advanced that the pox originated from intercourse with a mare having glanders Sydenham (1624–1689) thought yaws was carried to the New World by negroes from Africa, and there became syphilis and so came back to Spain but Lister (1684) thought it might have arisen in America from eating iguana Again the theory rose that syphilis came from fermentation of the seed ' in a prostitute but Astruc (1684–1766) threw it overseas again although Sanchez (1699–1783) suggested syphilis arose de novo in Europe and de Sauvages (1706–1767) said the treponematosis of Africa yaws was sui generis Gunner and Sprengel in the 18th Century sep arately advocated the Moorish African origin of European syphilis, and Sprengel thought yaws the original form[46]

Shrank (1834) thought syphilis was ancient but became malignant at the end

lected was the law of perspective for as they looked back 400 years what seemed to be a point of time was in reality an era

Treponematosis of Africa yaws was and is biologically free a juvenile disease unhampered in propagation, universally acquired and untreated Modern syphilis is biologically fettered to a small segment of the population confined to one type of propagation and continually subjected to the hazards of cleanliness and treat ment In the large continental mass the jump from the first pattern through the transitional period into the modern pattern of European syphilis required cen turies One cannot look back to a given date such as 1492 and say here it was that modern syphilis began an infinite series of overlapping stages has resulted in the present picture of syphilis For some reason it seems particularly distaste ful to syphilologists to trace modern syphilis back to an ancient disease of man and to regard it as the product of the interaction between the mores of modern life and the treponematosis of primitive peoples They must have a dramatic entrance for their disease upon the stage of history Certainly the syphilis seen in Europe and the United States today never has existed previously on this earth but neither has the civilized social pattern in which it exists Its distinctive characteristics are so much due to the habits of civilized man and to his medical profession that it may be properly regarded as an artificial disease in the sense that civilization itself is artificial If the gains of civilization were to be sud denly lost in some great cataclysm syphilis would revert to its biological juvenile form The promiscuous propinquity of primitive peoples results in a treponema tous exanthem among the children The promiscuity of cleanly well to do scientifically treated people results in a venereal disease of adults such as we see today

Most syphilologists have never seen the uninhibited treponeme at work in a primitive population as in yaws and those who have done so dismiss it as an exotic disease at best a cousin of syphilis Yet there is greater difference between the asymptomatic Wassermann positive syphilitic of today and Hutchinson s patients in London only 50 years ago than between his patients and the victims of Central African yaws The difference between 50 years ago and now is a matter of improved diagnosis and treatment Boyd s sage remarks about malaria may be applied mutatis mutandis to modern syphilis He says Since the introduc tion of cinchona comparatively few physicians have had the opportunity to ob serve the natural evolution of malarial infections to a spontaneous termination Now in the foregoing one should read arsenicals in place of cinchona and syphilitic in place of malarial and proceed This is in striking contrast to typhoid for example for which the lack to date of any specific bactericidal agent prevents the physician from brusquely interrupting the evolution of the disease Hence in the period since the beginning of specific medication the personal ac

indications that despite the prestige of orthodox opinion, supported as it is by the editorial policy of the publications of the American Medical Association the flow of opinion is away from the parochial Pusey view and toward Holcomb's 'evolutionary perspective' of treponematosis Castiglioni reflects this trend in his conservative conclusion 'Sudhoff demolished much of the flimsy evidence that connected its sudden spread with the return of Columbus sailors One should accept that syphilis was probably noted in Europe before the return of Columbus and that the doubtful allusions of early writers really refer to syphilis" But this historian is not yet quite off the fence for he adds that perhaps it was brought back from the New World in more virulent form!

Studies in Diagnosis

" he will say to himself that he has no right to give names to objects which he cannot define"

Darwin, *Descent of Man*

In the preceding historical review treponematosis has been described as a disease which displays itself in one of three patterns, depending on the local environmental circumstances and mode of propagation In a primitive community in a hot moist climate the principal early manifestation is a skin eruption of the yaws type in the child population In a more temperate climate and under more civilized conditions the universality of juvenile infection decreases, the eruption appears as much on the mucous membranes as on the skin and there are adult genital as well as extragenital infections This, the transitional type, is today found in China and parts of Russia as well as in the so called native syphilis of Africa and elsewhere This was the kind of treponematosis found in Europe in the 16th Century and still referred to as "medieval syphilis" The third pattern, the modern adult venereal form, had not yet made its appearance at that time but it was to be the product of evolutionary factors already at work in civilization For treponematosis in Europe was undergoing an evolution parallel to the evolution of human society In this process the generalized juvenile infection was to fade out entirely infection limited to 10 or 15 per cent of the adult population was to become the rule congenital transmission was to increase, and cardiovascular and neurological lesions were to become common In other words, the syphilis of today was in the making

Bloch and Pusey were not altogether wrong in saying that syphilis was a new disease about the time of the Renaissance for with improvement in hygiene and elevation of the economic level of the common people of Europe modern syphilis began to take shape about that time What these two and others like them neg

lected was the law of perspective for as they looked back 400 years what seemed to be a point of time was in reality an era

Treponematosis of Africa yaws was and is biologically free a juvenile disease unhampered in propagation universally acquired and untreated Modern syphilis is biologically fettered to a small segment of the population confined to one type of propagation and continually subjected to the hazards of cleanliness and treatment In the large continental mass the jump from the first pattern through the transitional period into the modern pattern of European syphilis required centuries One cannot look back to a given date such as 1492 and say here it was that modern syphilis began an infinite series of overlapping stages has resulted in the present picture of syphilis For some reason it seems particularly distasteful to syphilologists to trace modern syphilis back to an ancient disease of man and to regard it as the product of the interaction between the mores of modern life and the treponematosis of primitive peoples They must have a dramatic entrance for their disease upon the stage of history Certainly the syphilis seen in Europe and the United States today never has existed previously on this earth but neither has the civilized social pattern in which it exists Its distinctive characteristics are so much due to the habits of civilized man and to his medical profession that it may be properly regarded as an artificial disease in the sense that civilization itself is artificial If the gains of civilization were to be suddenly lost in some great cataclysm syphilis would revert to its biological juvenile form The promiscuous propinquity of primitive peoples results in a treponematous exanthem among the children The promiscuity of cleanly well to do, scientifically treated people results in a venereal disease of adults such as we see today

Most syphilologists have never seen the uninhibited treponeme at work in a primitive population as in yaws and those who have done so dismiss it as an exotic disease at best a cousin of syphilis Yet there is greater difference between the asymptomatic Wassermann positive syphilitic of today and Hutchinson s patients in London only 50 years ago than between his patients and the victims of Central African yaws The difference between 50 years ago and now is a matter of improved diagnosis and treatment Boyd s sage remarks about malaria may be applied mutatis mutandis to modern syphilis He says Since the introduction of cinchona comparatively few physicians have had the opportunity to observe the natural evolution of malarial infections to a spontaneous termination Now in the foregoing one should read arsenicals in place of cinchona and syphilitic in place of malarial and proceed This is in striking contrast to typhoid for example for which the lack to date of any specific bactericidal agent prevents the physician from brusquely interrupting the evolution of the disease Hence in the period since the beginning of specific medication the personal ac

quaintance of medical men with the natural history of this disease (has) greatly deteriorated "[13]

No one ever sketched or photographed Eohippus from life in the early Eocene, but geologists gathered fossils of certain ungulates in American tertiary formations and set them in a sequence and the theory of the evolutionary development of the modern horse was accepted[33] In the same way all the intervening and transitional steps between yaws and paresis can be demonstrated in European history within the compass of a few centuries along with occasional lapses when the course of events temporarily reversed itself Is it reasonable to oppose a similar view of progressive evolution in the story of treponematosis?

As long as treponematosis was generally of juvenile character, the local name in each country sufficed but as the venereal type emerged, clinical differentiation from the original treponemal matrix became necessary In the course of time the venereal disease ran away with Fracastoro s fanciful and meaningless word syphilis and in 1761 de Sauvages described yaws in Africa as a disease in its own right thus signalizing a differentiation which persists to this day In the light of the clinical concepts of his own time de Sauvages had a right to call yaws and syphilis by different names because they looked and acted like different diseases For example yaws must be different from syphilis, he said, because the first lesion does not occur on the genitals more frequently than on other parts[1] The two patterns of treponematous infection had now become so distinct that clinical diagnosis required a name for each in medical literature, and this was provided on the one hand by syphilis and on the other by yaws frambesia or pian

Yaws did not come into use in English as the generic name for juvenile treponematosis until sometime after 1800 and is, therefore, a relative newcomer in medical literature This is a fact which needs emphasis, since many have written as if the name yaws and the differentiation represented by yaws and syphilis were matters of antiquity As a matter of fact the differentiation was made more than 400 years after the first slaves were brought by the Portuguese from Africa to Europe and after the slave trade between Africa and the New World had been going on for 300 years Yaws before the 18th Century was just a native African name for a repulsive, eruptive disease that Oviedo called bubas, and which as leprosy went with the sailors of Lisbon and Cadiz when they returned to their homes in Brittany, Normandy Holland and the Scandinavian countries[94 110] Sydenham (1624–1689) wrote of yaws "It seems to me that the disease was brought into Europe by Spaniards who first contracted it from negroes they had purchased in Africa And as far as I can learn this disease, which so frequently attacks these miserable people does not at all differ from that we call the venereal disease with respect to symptoms—pains ulcers etc, allowing for a diversity of climate But it goes under a different name for they entitle it the

yaws Nor does their method of treatment differ from ours for they carry it off with a salivation raised by quicksilver '[118]

Many writers who are reluctant to admit the existence of syphilis in Europe before 1492 show a surprising willingness to ascribe great antiquity to yaws a disease which was described as sui generis only in 1781 Of course what these writers mean is that the nonvenereal juvenile type of disease now known as yaws is of ancient and probably African origin Manson[65] apparently believed this to be the case Chambers says indications point strongly to Africa but yaws may have been indigenous in any tropical country with accommodating climate and a primitive people He thinks some Biblical descriptions are suggestive of yaws it may be related to Arabic leprosy possibly yaws was the disease described as safat by Haly Abbas (about 900) and negro slaves brought it from Africa to Jamaica Scott thinks yaws probably was autochthonous in Hispaniola Brazil Fiji Samoa and West Africa and imported into the West Indies by slaves[111]

Columbus found the natives of the Islands too proud and not robust enough for general labor If plantations were to be made a new source of labor was necessary[1 7] Since Portugal held the key to West Africa and was already deeply engaged in running slaves to Europe she was given a trade license (contract) by Spain The first slaves to land in Hispaniola came in 1502 just 10 years after Columbus set foot there In 1518 there was exten ion of the contract to bring 4 000 annually Sugar cane culture was introduced from Cape Verde by Columbus in 151 or possibly from the Canaries by Aguilar in 1505

At first all sl ves were taken from Africa to the West Indies via Europe so as to ' christianize them but in 1562 John Hawkins hijacked 300 slaves from the Portuguese and sold them directly to the Spanish in Hispaniola Over a century later 1713 the English took over the contract (monopoly) agreeing to furnish the Spanish colonies with 144 000 in 30 years They took more than double this number in the first o years and between 1733 and 1,66 the average annual import was 20 000 There was a high mortality but importations continued to offset deaths until a total of over 2 000 000 had crossed from Africa as slaves The first negroes to be brought to the continent came in 1619 and in 1801 the total colored population of the North American mainland was over 1 000 000

As Scott says There can be no doubt that importation of infected slaves would contribute much toward spreading the disease for it is known that epidemics (sic) of it occurred on slave ships Fresh cases constantly arriving were isolated in yaws houses there was confusion between yaws and leprosy and the same stockades were used for both

The chronology of events for the two decades just before and just after 1500 offer perplexing problems to those who feel they must regard syphilis and yaws

as distinct diseases, and to those, who maintain the American origin of syphilis Events in those days were moving very fast An illustration of the dilemmas encountered is provided by one writer who says, 1) there is overwhelming evidence that syphilis came from the New World, 2) yaws is probably older than syphilis and did not appear with the same dramatic suddenness, 3) if syphilis came from yaws then yaws must have been in the Indies before Columbus, 4) there is no evidence of this 5) yaws, however was present along the West Coast of Africa and was carried to the West Indies with slaves after 1502, 6) but yaws was not carried by slaves to Portugal between 1442 and 1492 although the annual importation came to 7 000 or 8,000, 7) Oviedo gave the first clear description of yaws under the name of bubas

Thus black African slaves, who had been coming to Europe by tens of thousands for 50 years, had not brought thither any yaws, but slaves from exactly the same place began bringing yaws to Haiti from the time of their introduction there in 1502 Syphilis just barely got away from the New World to Spain and Portugal in 1493–1502 in time to avoid collision with yaws on its way west from Africa Oviedo described something he called bubas, was it a) syphilis carried west by the Spaniards or carried east by the Amerinds or was it b) yaws autochthonous in Haiti or imported from Africa?

Another writer[34] takes the following modified view It is probable that syphilis first came to the Western Hemisphere with Columbus, found a completely non immune Amerind population and exacted its heavy toll Yaws was introduced with the importation of negro slaves from Africa That is, we are to believe that a disease, which 40 years later was to be named syphilis (what it was called at the time is not stated) went west with the Spaniards and arrived in the Western Hemisphere just a few years ahead of another disease later called yaws which came with black slaves from Africa Does this mean there were two new diseases introduced from Old to New World about the same time? And if so are we to understand that they retained their identity throughout the subsequent years and did not get scrambled with each other or with a possible autochthonous treponematosis in the West Indies?

These writers are illustrative of many who have felt impelled to accept as true certain dogmas as to the origin of syphilis and the relation of syphilis and yaws Their ingenuity in fitting the known facts to these theories has been boundless, but in sum they cancel out

There is apparently one fact upon which all are agreed an enormous amount of treponematous infection came from Africa to the West Indies and later to the southern United States This was of the juvenile nonvenereal type and in places such as Haiti where the climate and mores of the New World approximated those of the Old the disease did not change its pattern Indeed, it retains the same

character on that island today Where the climate was colder however and in circumstances where a measure of clothing and cleanliness was introduced the juvenile form shaded into the transitional displaying mucous membrane lesions and venereal as well as nonvenereal epidemiology

Charleston S C became a great slave port and market for the mainland Fanny Kemble in her Journal[1 7] described the squalid condition of the slave children apt environment for the childhood exanthem The Indians said John Clayton[15] in a letter in 1687 had yaws and Byrd in North Carolina in 1728 speaks of whites as well as colored people having yaws He says The truth of it is the inhabitants of North Carolina devour so much swine s flesh that it fills them full of gross humors For want too of a constant supply of salt they are commonly obliged to eat it fresh and that begets the highest taint of scurvy Thus whenever a severe cold happens to constitutions thus vitiated it is apt to improve (sic) *into the yaws called there very justly the country distemper This has all the* symptoms of syphilis with this aggravation that no preparation of mercury will touch it First it seizes the throat next the palate and lastly shows its spite to the poor nose of which it is apt in a small time treacherously to undermine the *foundation This calamity is so common and familiar here that it ceases to be* a scandal and in the disputes that happen about b auty the noses have in some companies much ado to carry it [17]

Dr John Brickell who practiced medicine in Edenton about 1731 wrote of gonorrhea and syphilis Clapp and French Pox are common Distempers in Carolina He said of yaws The Yaws are a Disorder not well known in Europe but very common and familiar here it is like the Lues Venerea having most of the Symptoms that attend the Pox but is never attended with a Gonorrhea in the beginning This Distemper was brought hither by the Negroes *from Guinea where it is a common Distemper amongst them and is communicated* to several of the Europeans or Christians by their cohabiting with the blacks by which means it is hereditary in many Families in North Carolina and by it some have lost their Palates and Noses [17]

There was contemporary discussion as to the relation of yaws and syphilis In Medicine in Virginia[1] in 1773 conversation at table included discussion of cachexes or yaws which is a violent form of scurvy and the statement (one can imagine the speaker s air of finality) As a matter of fact though very prevalent in Africa and other tropical countries yaws is not a venereal disea e at all Yet some people including whites were contracting yaws venereally De Bow said yaws which was not a venereal disease among the Africans was begun to be called so among negro slaves He said this modified form of yaws was commonly mistaken fo syphilis in Mississippi and Louisiana It is a contagious disease communicable by contact among those who greatly neglect cleanliness

Children are liable to it as well as adults" He said it was sometimes called pseudosyphilis, if contracted by a white, it attacked first the nose and throat in a fashion very similar to syphilitic affections without previously having appeared on the genital organs[1] [7]

There is no doubt that much yaws came to the North American continent over a period of several hundred years, yet yaws as such disappeared What became of it? There were various contemporary theories for this paradox no better and no worse than those of today Chambers (1938) says yaws is unable to get a hold in temperate countries and does not thrive north of the isotherm of 80° F but he quotes Spittel who says yaws does not attack Europeans or for that matter any cleanly living individual, whatever his race Rat[1] believed that cold intensified (sic) the action of the syphilitic virus A modern writer says the treponeme of yaws is more susceptible" to cold than that of syphilis and he looks for some as yet undiscovered factor to account for failure of yaws to persist along our Gulf Coast

What do these writers mean when, like Manson, they say the spirochete of yaws cannot persist in temperate climates? Yaws is an internal disease of man, and the internal temperature of man does not vary from one latitude to another Did not Manson mean that yaws cannot persist on the skin? This is true and neither can it persist on the skin in a dry climate, or on a skin that is well clothed and washed occasionally What happens to the treponeme of yaws when it gets on a clothed, clean, dry skin in a temperate climate? Manson said that it dies and that is the end of the disease as if the spirochete were an ectoparasite like Sarcoptes or Pediculus, but the parasites of yaws are distributed throughout the patient s body, not confined to the skin Yaws like all treponematosis is a constitutional disease and not a mere skin infection like impetigo Its exanthem must be recognized as but the outward sign of the inward infection Query Where is the spirochete found, if the skin of the trunk is too cool and dry? Ans In the moist folds of the body Q Where does the eruption appear, if the skin as a whole is too clean, too cool and too dry? A On the mucous membranes And in the meantime the typical internal pathology continues on its way in dermis glands blood vessels and bones irrespective of environmental temperature The remarks quoted above imply that yaws cannot persist becau e the spirochete gets out on the skin and dies and then like a plant stripped of its leaves the whole infection dies Put in this fashion the absurdity of this viewpoint in the light of modern concepts becomes obvious

It is not essential for survival of the treponeme of yaws that it should have an occasional excursion to the fresh air of the epidermis but perhaps Manson meant to say it is essential for the propagation of the disease, that is that yaws is only contagious through skin contact According to this view the disease would be

bottled up in its victims in a temperate climate and would die with them The facts are against this view Treponematous infection is not so easily arrested When skin to skin contact is broken and the treponeme can no longer persist on the skin its activity expands on the mucosae This indeed was the fate of the yaws which disappeared on the North American continent By a simple process of adaptation to a change in environmental conditions the yaws of the black slaves became a portion of the venereal syphilis of the South In some places the conversion was rapid in others slow much depending on accompanying changes in living habits and economic levels In certain parts of the South today there still remain strong foci showing the characteristics of the transitional phase a high incidence of syphilis in the community many extragenital and childhood infections a profuse mucocutaneous eruption as well as typical cases of venereal history and consequent chancres Such was the situation in Macon County Alabama in 1930 when a survey showed that 39 8 per cent of the population had positive Wassermann reactions and only 3 per cent of positive cases had had any treatment In this county were found extremely low levels of literacy and of economic social and cultural status [5] Throughout the most of the South however the venereal pattern of epidemiology is now predominant

Fox said that yaws cannot come to the United States because it is a tropical disease On the contrary it can come and has come in huge quantities but when it comes it does not remain yaws but becomes syphilis He says if yaws ever got started in the South we should know how to control it The public health problem however is not so much the control of the imported yaws as the control of the venereal syphilis which results Fox s view involves the fallacy of petitio principii another writer similarly begs the question in the following quotation Yaws is chiefly a disease of negroes chiefly because of the geographical distribution of the disease it practically never invades temperate zones [6]

Differential Tables

When yaws and syphilis were first differentiated 150 years ago diagnosis was based on history and inspection The germ theory of disease was only faintly formulated and etiological concepts still were primitive Classifying infectious diseases on the basis of their causes now a universally accepted principle was then unheard of In the succeeding years skin diseases among which treponematosis fell were divided into an elaborate classification based upon lesion morphology and using many meaningless personal names (Much of this philosophy of classification remains in dermatology to this day) Little account was taken of the possibility that the appearance of a lesion might change with a change of environmental conditions Diagnostic concepts were rigid For example pathognomon

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found only in the tropics and among the poor syphilis is only rarely epidemic but yaws is both endemic and epidemic These cannot be admitted as differential points however since they depend on the climate and the habits of man influences extraneous to the treponeme Obviously venereal treponematosis may occur anywhere in the world whereas the nonvenereal is confined to certain locales and Rat has not differentiated them when he says syphilis is venereal and yaws non venereal

Rat s differential regarding the usefulness of mercury and iodides is now abandoned No one any longer attempts to diagnose one condition from the other by their different response to mercury bismuth the arsenicals or any other drug including in our day penicillin Rat says yaws and syphilis do not protect against each other but some degree of mutual protection is now universally admitted as will be seen later That secondaries do not itch in syphilis and that syphilitic gummata are in three zones in distinction to the vascular granulations of yaws are points no longer meaningful

Under the acquired heading Rat enumerates 11 features of syphilis which he says are not found in yaws but in all cases further knowledge has shown either that they are not always true of syphilis or that they may be true of yaws thus invalidating their differential significance These 11 points are 1) indurated primary with adenopathy 2) phagedena of primary 3) polymorphous secondary 4) eruption sometimes pustular 5) mucous membrane lesions nearly always present in secondary stage 6) alopecia 7) iritis choroiditis retinitis orchitis 8) specific adenopathies 9) ulcers of tongue anus rectum 10) paralysis of ocular muscles 11) malignant type with pronounced cachexia

Under hereditary Rat lists 9 of the common stigmata of congenital syphilis Since such transmission only occurs in syphilis under certain conditions and inasmuch as the juvenile feature of yaws accounts for its usual failure to exhibit such transmission these stigmata do not posse differential significance Finally Rat stres es 1) that secondaries appear on the front of the trunk in syphilis and seldom in yaws 2) that gummata appear on the face and upper chest front and back in syphilis and mostly on legs and lower arms in yaws and 3) that in syphilis the majority are infected in their twenties and thirties whereas the majority of yaws infections occur before puberty No one today would advance the fir t two points and the third obviously is not concerned with etiology but with epidemiology

In this table therefore an experienced clinician has failed to adduce a single point capable of being used as a touchstone to differentiate in a given case whether the diagnosis should be syphilis or yaws At Rat s request Sir Jonathan Hutchinson wrote a preface to his book and took the opportunity to expound the point of view contrary to Rat His arguments are especially interesting as they arose from

significance was attached to the kind and color of crusts, or as to whether a disease was acquired in childhood or adult life, as if it made any difference to the diagnosis what the patient's age was. Apparently it did not occur to the diagnosticians that a disease might occur in children in some places and in adults elsewhere. These are merely illustrations of a point of view, which still colors the thinking of many in regard to treponematosis, a feeling that the shape and size of a lesion is of more diagnostic importance than its bacteriology and a failure to distinguish clearly between epidemiology (environmental conditions) and etiology (causal agents).

Attempts have been made for 150 years to differentiate between yaws and syphilis. In the course of time innumerable points of difference have been cited, but not one when examined critically has signified a qualitative difference. It has never been possible to say: to this line is yaws, beyond it is syphilis. There has always been a shading off and overlap between them. The differences have been quantitative: yaws is more of this and less of that and syphilis vice versa. The desire of the majority of the medical profession to establish a qualitative difference between yaws and syphilis has been as keen and as unrewarded as the old mathematicians' search after the formula for squaring the circle. During the golden age of bacteriological discovery many predicted that the difference would be plain when the specific germs of the two diseases were discovered. This hope has been completely dashed. Then in the serological era the blood tests were expected to do the trick, but again no difference has appeared. Then it was thought the two conditions could be separated by pathological studies and finally by biological tests, but these have given equivocal results.

It is important to review the history of the differential tables during the past 50 years, keeping always in mind that what is required is some characteristic feature or property of one condition which is not found at all in the other. If a protest is raised that this requires too much, the reply is that it is no more than any other critical differentiation. Falciparum malaria has crescentic gametocytes, typhoid fever gives a positive Widal with *Eberthella typhosa*, *E. histolytica* has a quadrinucleate cyst, mumps affects certain organs of the body. These things are true of each disease respectively and not true of other diseases. Differential points rapidly lose their differential value if they bracket two conditions. One may even say that if a given point fails to differentiate in 5 per cent of a group of cases, that point has lost 95 per cent of its differential value, because in a given case one would never know whether the "differential" was working or not.

The first "modern" differential table was set up by Numa Rat[105] in his book on yaws published in 1891. Here is a man discussing yaws and syphilis more than a decade before the "spirochete and Wassermann" age. He divides his differential points into three classes: general, acquired and hereditary. Under the general heading he says that syphilis occurs in all latitudes and classes, whereas yaws is

solely that the more characteristic chancres are encountered Finally he dismissed 7) the statement that there was any recognizable difference in the adenopathy of syphilis as compared to yaws or 8) that one of them was any more susceptible to spontaneous cure than the other

Further quotations from Hutchinson are as fresh and reasonable today as they were the day they were written more than 50 years ago He says 'It is quite certain that in the same community syphilis does receive modifications from the peculiarities of constitution of those in whom it occurs It is easily conceivable that transmitted from person to person through many generations in one and the same race (the Singhalese or the Negro for instance) the disease might acquire some minor persisting feature of difference It is possible that parangi in Ceylon and yaws in Africa may be syphilis so modified We should be going however much further than any facts in our possession warrant if we were to suppose that syphilis so modified could become a disease capable of existence side by side with its progenitor in an independent position If we are to understand that syphilis runs its usual course in a patient who has recently suffered from yaws and vice versa then we have clinical proof that the two have attained specific distinctions and at the same time most will I expect be willing to admit that it becomes extremely improbable that the two have ever within historic periods been other than specifically distinct But if this is accepted it would certainly follow that we should expect that they would no longer be restricted to race or locality Yet in support of the belief that yaws cannot possible be anything else than syphilis we have the fact that it never comes to Europe It seems impossible that a very contagious malady of prolonged duration to which whites as well as colored persons are liable which prevails over such extensive areas with which commerce is so extensive should remain for centuries restricted to its own districts So far as we yet know yaws in passing the ocean transforms itself into common syphilis We have no other instance of a specific animal poison which is restricted in its operation by race and climate 'Whenever an Englishman contracts yaws abroad he comes home with syphilis [4]

Hutchinson was far ahead of his times All others were so impressed by the different appearance of the two conditions and so convinced of their own ability to tell them apart that they missed Hutchinson s profound observation that yaws and syphilis were not different diseases but different patterns of the same disease When Schaudinn in the early years of this century discovered *Treponema pallidum* immediate search was made for a similar germ cause of yaws and when it was found great efforts were made to find some constant morphological difference It was at first thought to be thinner and hence the specific name *pertenue* What was in the minds of those who gave this parasite a distinct specific name?

the experience of a man of Rat s own times and one who had had as wide an acquaintance with syphilis as anyone in that period

Hutchinson [6] lists 6 points which he thinks favor the identity of yaws and syphilis as follows 1) similarity of stages 2) resemblance between the tertiary stages in character and time 3) identity of treatment, 4) common characteristics in the secondary eruptions 5) restriction of yaws to certain localities and 6) a common tendency to papillary outgrowths Under the fifth point he says, No Englishman comes back to us the subject of yaws It would appear that it is a malady which cannot leave its home He never could get over the fact that yaws only appeared in certain locales Under the sixth point he says papillary outgrowths are by no means absent in syphilis as witness secondary lesions on the tongue and warts and condylomata on the skin

Hutchinson frankly faced 8 points, which were being used to oppose the identity of syphilis and yaws 1) The unanimity of opinion of local observers His words have application today, All the more recent observers who have studied the malady (yaws) in its native haunts are, I think, unanimous in the opinion that it is not syphilis The confidence with which this opinion is held depends, however to a very large extent upon impressions received by actual observation rather than upon facts which can be stated in print and submitted to the judgment of a reader having no personal experience of the malady ' Hutchinson was rightly skeptical of the men — and he acknowledged their number — who said I have seen syphilis and I have seen yaws and take it from me, they are different diseases He rightly demanded and felt he had not received a definite scientific statement of any difference which could be applied to settle the question of diagnosis in a given case 2) Yaws usually begins in childhood 3) Yaws is not inherited and is rare in the first year of life occurring mostly in the second quinquennium and next in the second decade These points he met as follows, " Syphilis is usually inherited from parents who have had the disease quite recently, and we are accustomed for practical purposes to limit the period of possible transmission to two years It is clear we ought not to expect hereditary transmission (in yaws) as a frequent occurrence when it is acquired at such an early age

Hutchinson was not impressed by the statement 4) that some of the phenomena of syphilis such as lesions of the mucous membranes in the early stages alopecia eye signs orchitis paralysis of the ocular muscles, are not met with in yaws H said they were far from constant in syphilis As to 5) the fact that yaws is not acquired through sexual intercourse he said this might very well depend on the habits of the people concerned He had the following to say about 6) the claim that the primary sore in yaws is never an induration ' Primary sores (in syphilis itself) occur erratically Many or even most of the erratic chancres of true syphilis are destitute of characteristic hardness It is on the genitals almost

Three writers of the 19th Century described mucous membrane lesions in yaws Maxwell [5] in the West Indies Daniels [0] in Oceania and Charlouis [3] in the East Indies Manson considered this a differential point but it was denied by Ramsay [1] in Assam Sellards [1] in the Philippines and Hackett in Australia Hackett also has demonstrated recently sections from the fauces of a 12 year old patient in Uganda with characteristic yaws skin lesions They showed thickening of the epithelial layer with infiltration of leucocytes and spirochetes of the syphilis yaws type in the collections of leucocytes in the thickened epithelium As has been said above the skin and mucous membranes in treponematosis have a reciprocal relationship in regard to the eruption If climatic conditions are so favorable that there is a profuse skin eruption there will be few lesions on the mucous membranes On the other hand if the treponeme can not tolerate the coolness and dryness of the skin the eruption in the folds of the body and on the mucous membrane becomes prominent This is true whether one is considering the yaws or the syphilis pattern of treponematous infection and does in no wise constitute a differential point

Fox admits that there is no differential significance in the symptom of itching or the signs of adenopathy He lists 6 clinical features however which he says characterize yaws as opposed to syphilis It should be noted that they either a) concern epidemiology and therefore do not apply or b) are not tru of all yaws or c) may be found in some forms of syphilis These features are 1) extragenital lesions 2) no congenital transmission 3) absence of mucous membrane lesions in secondary 4) rarity of central nervous system lesions 5) less visceral involvement in tertiary 6) no iritis or alopecia

Six years later in 1935 Williams made an exhaustive comparison of yaws and syphilis from the standpoint of the pathologist and reached conservative *conclusions There is he said unquestioned cross immunity between the two* conditions the bones present very much the same picture there are no aneurysms in yaws and the viscera are probably less involved there is a difference in the histology of the primary lesions less in the secondary and least in the tertiary It looked as if the discussion might be taking a turn from clinical symptoms and signs into the field of pathology but Chambers in his book in 1938 brought it back sharply by declaring that microscopical differentiation of the two conditions is fruitless

Chambers differential table is in the tradition of Rat listing 22 clinical symptoms and signs in which there is contrast Again many points such as childhood acquisition of yaws have nothing to do with etiological diagnosis and again Chambers in describing the yaws of Jamaica runs counter to the opinions of those familiar with yaws in other countries again distinctions of degree are adduced quantitative differences expressed by such phrases as not quite the same desqua

Simply the human fallacy of rationalization The argument ran thus Yaws and syphilis are different diseases, therefore they must be caused by different parasites, therefore although I must admit I can t tell them apart I shall give these two parasites different names and classify them as different species As a matter of fact this fallacy is the main if not the sole, argument advanced today for the retention of *T pertenue* A specific difference in '*T pertenue* cannot be or has not yet been, demonstrated it just *has* to be different

It was already apparent to Ashburn and Craig in 1907 that *T pallidum* and *T pertenue* were indistinguishable, so they took the position held strongly by so many ever since that one could be differentiated from the other 'only by a consideration of the lesion from which it is obtained or by the inoculation of certain animals' As to the question of animal inoculation more will be said later Meantime, these writers set up a clinical differential in the following terms Syphilis they said, produces a pleomorphic lesion with granulomata in secondary and tertiary stages, whereas yaws produces a uniform eruption with a granulomatous primary and a yellow crust Yaws, as well, is epidemic affecting children and not exhibiting genital lesions, alopecia or iritis None of these differential points would be considered valid today, and most of them are connected with the method of acquisition and the environmental conditions of the contagion These writers, like Rat were describing two patterns of a disease The identity of the parasitic cause had not given them the key to the diagnosis on the contrary, their obsession with the obvious differences between syphilis and yaws led them and most of their contemporaries to rationalize different names for two indistinguishable organisms It is a law of biological classification that organisms which can not be distinguished must be given the same specific name Contravention of this primary law accounts for the persistence of *T pertenue* to this day

The next differential table to be considered is that of Fox[37] in 1929 He admits that late cases of yaws and syphilis are indistinguishable and says the diagnosis in such cases must be made on the basis of 1) the history syphilis is venereal and yaws is nonvenereal, or 2) the residence syphilis is urban and yaws is rural The unreality of this classification is illustrated by the question suppose by chance yaws infection were acquired venereally in a city it would be syphilis, would it not?

Fox is impressed with the exaggerated tendency in yaws to fungation resembling the moist papules and condylomata of syphilis The explanation is that the moisture and heat of the climate provide opportunity for proliferation of the treponemata on the trunk of the body in yaws whereas in syphilis this opportunity is limited to the perineum and the folds about the genitalia Fox also stresses the almost total lack of mucous membrane lesions during the early period of yaws There are plenty of witnesses who disagree with him on this point

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mation, not so profuse eruption, usually indurated, usually genital, true of 56 per cent males and 75 per cent females, less frequent nerve lesions less common cardiovascular lesions, spinal changes less likely

It must be emphasized that no objection whatever is here made to these statements by Chambers By his own calculation he has seen 6,000 patients with active and 2 000 with latent yaws and is qualified to describe that condition Objection however, is made to the implication that by the use of his differential table one could tell whether a given case were syphilis or yaws One must have one or more points of which it is possible to say this is present, therefore this must be yaws In the mass and by and large anyone can distinguish yaws and syphilis They are patterns so clear that laymen can identify them, there never has been any difficulty about diagnosing patterns in medicine The difficult thing is to diagnose the individual and none of these tables will do that

Perhaps the most widely known differential table for yaws and syphilis is the one which has appeared in edition after edition of Manson's TROPICAL DISEASES In 1932 Blacklock[16] essayed an analysis of this table with the object of demonstrating that fallacies had been introduced ' chiefly owing to comparisons being made between things which are not properly comparable " He brought forward arguments against comparing yaws, which is mainly a nonvenereal disease of children in rural areas of the tropics, and which begins by an extragenital primary lesion, with venereal adult syphilis of Europeans ' The accounts ', he said, of adult venereal syphilis as it affects natives in tropical countries are not as yet complete, but so far as they go they indicate that such syphilis varies as greatly, in many respects, from venereal syphilis in adults in temperate climates, as does yaws The effects of extragenitally acquired syphilis in the native children of rural areas of the tropics are those about which we chiefly require information " In the decade from 1928 to 1938 appeared a series of papers devoted to bejel, the juvenile syphilis of the Euphrates Arabs[6] These to a certain extent provided the desired information and supplied factual support for Blacklock s more or less philosophical approach as will now be seen

I *Yaws not congenital Syphilis congenital* It is not just to compare adult venereal syphilis with yaws in this respect because as Stokes says, time diminishes the infectiousness of syphilis ' In bejel, a juvenile syphilis comparable to yaws congenital transmission is equally unknown

II *Yaws primary sore extragenital Syphilis usually genital* ' This highly esteemed differential criterion " said Blacklock, ' is no more than the statement of an epidemiological observation By the use of this identical formula, it is open to anyone who desires to do so to prove that acquired syphilis of infancy in England is an entirely different disease from venereal syphilis " He quotes Lacapere who says of syphilitic chancres among the natives of Africa, that

they are usually unrecognized often extragenital and occur frequently in children The picture in bejel is exactly the same

III *Yaws typical yaw pathognomonic furfuraceous and plantar lesions characteristic Syphilis seldom imitates frambesia* Blacklock by numerous quotations shows that opinion is far from unanimous among yaws experts as to what constitutes a typical or pathognomonic yaw or how frequently furfuraceous eruptions are found Plantar lesions by the law of syphilitic localization at points of trauma would certainly be more common in the bare feet of natives than in the shod feet of civilized people The frequency of succulent or furfuraceous skin eruptions and plantar lesions in bejel supports Blacklock s position in this respect also

IV *Yaws mucous membranes not affected Syphilis affected* Blacklock adds further illustrations to those given above to show that neither of these propositions is exact Bejel in the desert Arab is notorious for its mucous membrane eruption *but so also is the yaws of dry and mountainous districts*

V *Yaws itching common Syphilis itching rare* Here again there is disagreement among the experts in the two conditions both as regards the primary lesion and the secondary eruption Itching certainly is not characteristic of juvenile syphilis in the form of bejel

VI *Yaws alopecia not known Syphilis it may occur* As Hutchinson says syphilitic alopecia is by no means common Baldness in the native from any cause is seen rarely certainly it is no more found in the native child with bejel than in the native child with yaws

VII *Yaws eyes unaffected Syphilis iritis common choroiditis and retinitis rare The evidence in comparison of yaws and venereal syphilis is equivocal* The comparison of yaws and juvenile syphilis (bejel) shows that the eyes are equally unaffected

VIII *Yaws visceral lesions absent Syphilis visceral lesions occur i e pericellular cirrhosis gumma of liver kidneys etc* Blacklock quotes observers *of colonial syphilis to the effect that one of its characteristics is the great rarity* of visceral lesions Colonial syphilis is a descriptive name for what has been called above the transitional phase He says Yaws as regards its visceral lesions ought properly to be compared with syphilis in the tropics occurring among children When comparison is made between yaws and bejel visceral *lesions are found to be equally rare*

IX *Yaws nervous system never seriously affected Syphilis nervous system prone to infection tabes general paresis of the insane* The parenchymatous lesions of the central nervous system are admittedly rare in yaws and this is also true of juvenile syphilis (bejel) This does not mean that in yaws and bejel the *neuraxis is not invaded* Moore[91] says *If during the first months of the disease*

organisms are more or less constantly present in the blood it is difficult to understand how invasion of the nervous system does not occur Evidence (shows) that such invasion does take place in the majority of cases, probably by vascular involvement of the meninges parenchyma or both Whether or not clinical neurosyphilis will develop must depend partially upon the extent to which the individual patient reacts against his infection That most patients do succeed in dealing spontaneously with this neurological invasion is evidenced by the comparatively small numbers of clinical neurosyphilitics ' Sequeira says[111] ' it is worthy of notice that African races suffering from widespread syphilis rarely show either general paralysis of the insane or tabes, and they are almost untreated Von Duhring[1] found the same fact in the rural and juvenile syphilis of Turkey it is also true of bejel

Blacklock mentions three groups of factors which have been advanced to explain why as Osler and McCrae said in 1928, civilized people are those who get paresis These are 1) occupation which comprises perhaps intellectual trauma and hypertension 2) race and 3) the influence of the early eruption Moore says An extensive profuse secondary syphilis of the skin apparently protects the patient against late CNS involvement (and vice versa) Likewise, the individual who becomes hypersensitive (allergic) to his own organisms and who develops gummatous late lesions of the skin mucosae or bones is less likely to develop neurosyphilis (and vice versa) ' It cannot be a matter of neurotropic strains because Europeans who contract syphilis (or yaws) from natives, exhibit central nervous symptoms[113]

There is a fourth factor which may play a part in preventing parenchymatous neuropathology in yaws bejel and other juvenile forms of treponematosis Syphilitic infection occurs in an adult at one moment of time His contact with treponemes in general is extremely limited On the other hand the juvenile infections appear early in life as a result of massive contact Furthermore, that contact is by no means broken when the individual has gone through his early stage but continues throughout his life An individual living in a yaws or bejel community is continually subjected to contact with treponemes small increments of parasites are continually invading (and vaccinating ?) his body In this may be found the true explanation for the paradox which has puzzled everyone, namely why tabes and paresis are most common where syphilis is least widespread and why they are not found where there is most treponematosis, why they should be concomitants of the period in man s history when he has been most thoroughly armed with knowledge preventives and remedies against the disease

X *Yaws no endothelial proliferation as in syphilis Syphilis endarteritis obliterans of viscera cerebral thrombosis* This topic will be discussed more fully in the next section Suffice it here to quote Blacklock s statement ' Sweep

ing conclusions have been arrived at as the result of the examination of a very limited amount of material (and) many of the conclusions reached are based on comparisons of the wrong material

XI *Yaws better resisted constitutional disturbances slight Syphilis attacks constitution affecting vital structures* As Blacklock says if affections of the viscera central nervous system and cardiovascular system are here intended other sections have disposed of these as points of differentiation between yaws and syphilis If reference is made to the cutaneous and osseous manifestations of the two conditions a great many people will agree with Branch when he says that if syphilis and yaws are different diseases then yaws is the worse of the two

In this connection opportunity is presented to point to a fallacy which is all too common in discussions of the history of treponematosis The following statement by Rolleston is illustrative Syphilis when it breaks out in a previously uninfected race is much more virulent than in civilized and syphilized countries but the much milder syphilis (which we now see) in this country can hardly be ascribed solely to immunity as the influence of early recognition and treatment must be taken into account Terrible tertiaries are now seldom seen Let us analyze this The author refers to virulent syphilis and by this presumably he means profuse eruptions ulcers bone lesions and terrible tertiaries such as gangosa but these are seen most frequently in the oldest homes of treponematosis not in the newest It is a matter of personal opinion which is worse the gangosa of Africa or the paresis of Europe but it is juvenile acquisition and lack of treatment and not the newness of the disease that cause profuse eruptions and terrible tertiaries The unmodified biological disease is always that way When it becomes limited to a few comes under treatment and becomes an adult disease t becomes less spectacular to the eye and is characterized by internal parenchymatous degeneration Rolleston and Manson cannot both be right Which is milder?

XII *Yaws does not respond to mercury Syphilis responds well* The fallacies underlying these statements need no discussion This is a position now abandoned by the most ardent differentiators

Pathology and Cross immunity

It has been claimed that the various forms of treponematosis such as yaws syphilis bejel and pinta can be distinguished by the histopathological pictures which they respectively produce The general tendency of late however is to admit that the underlying processes are fundamentally the same and that the differences are quantitative rather than qualitative This means that there is no

one histological criterion of sufficient magnitude, constancy and universality to establish a differential diagnosis in a given case

Goodpasture[46] in 1923, describing the skin changes in yaws, said treponemes were demonstrated in great numbers in the perivascular tissues about the terminations of the papillae, for this and other reasons he thought the secondary yaw began there and spread thence to the epidermis where conditions of growth subsequently were more favorable Conner [7] described the histological picture of syphilis as a perivascular plasmoma and called attention to the papillomatous overgrowth in the condyloma This is of the same nature as the common papillomata of yaws The difference in climatic conditions explains why they tend to profusion on the trunk and face in yaws and are limited to the folds of the body and to the mucosae in transitional and venereal treponematosis Hutchinson [0] noted this tendency to overgrowth in syphilis, mentioning as examples, 1) hypertrophied papillae on the dorsum of the tongue and in condylomata, 2) thickening of the intima in arteritis and 3) hypertrophic sclerosis with diffuse fibrous overgrowth Of the same quality is the tendency in yaws and juvenile syphilis (bejel) to hyperkeratosis of the soles when shoes are not worn

Conner mentions other characteristics of syphilitic lesions, and these also are shared with yaws, the symmetrical distribution the circinate outline the tendency to hyperpigmentation in healing followed by depigmentation and atrophy of the skin and the development and persistence of treponematous lesions at sites of irritation

For a time it was the vogue to link ' *T pertenue* with ectodermal pathology in contrast to *T pallidum* Hoffmann [0] said in 1936 The essential difference is that *T pertenue* invades the ectoderm and *T pallidum* the mesoderm ' Fox[33] in 1938 said *T pertenue* was ectodermoblastotropic (sic) whereas *T pallidum* was panblastotropic Hasselmann reached the height of absurdity in this matter by stating that yaws was only a skin disease in contrast to syphilis which affects all parts of the body We know with Moore[91], however that the treponemes by whatever name they may be tagged circulate in the blood to all parts of the body, producing lesions from the inside

Differences in the pathological picture are due to difference in degree and not in essence the blood vessels are involved more here than there the acanthosis is more marked or less marked, the leucocytes are more, or they are less numerous, the corium is more or it is less, infiltrated with lymphocytes, plasma cells spindle cells there is more or less, edema The part, which secondary infection plays in the characteristic picture of yaws, has been discussed by several writers Butler[1] took the categorical position that *T pallidum* never evokes a polymorphonuclear response and never liquifies the tissue cell Goodpasture[46], however, believed the edema and at least some of the leucocytes were due to the trep

onemata in the dermis although he quotes Siebert as believing that the trep onemata in yaws migrate to the epidermis attracted by the leucocytic response to cocci in the surface layers of the skin The rapid disappearance of the exudate of the secondary lesions under neoarsphenamine suggested to Goodpasture that it was of treponemal and not of coccal origin Ferris and Turner [5] found areas of great polymorphonuclear abundance but no phagocytosis or any evidence of or ganisms inside cells even in the epidermis In these areas there were no bacteria either before or after 1 neoarsphenamine treatment

Williams[1 1] however speaking of yaws lesions says that leucocytes invade the epidermis in great numbers there are areas of necrosis small abscesses and good sized colonies of gram positive cocci suggesting an important role for second ary infection (One of the outmoded differential points is the yellow crust on yaws papillomata Undoubtedly this was dried serum colored yellow by pus associated with these secondary pyogenic invaders) Here again one need not be disturbed by discrepancies in the descriptions of various authors Doubtless they may be at tributed to the use of material from different sources and different parts of the world

Williams[1 1] says of tertiary or late forms that there is little if anything to distinguish the histopathology of yaws and syphilis The essential feature is a granuloma with considerable variation within both entities Blacklock[10] calls attention to the fact that the gumma of syphilis is considered by most observers to involve endarteritis as a precursor of necrosis and since gummata are a charac teristic feature of late yaws we are obliged either to admit that obliterative endar teritis does in fact occur frequently in yaws or else postulate that the histopathol ogy of the cutaneous gumma of yaws is entirely different from that of the cutaneous gumma of syphilis which no one would be willing to do Hallenberger is quoted [5] as believing that absence of caseous necrosis is characteristic of the gummatous lesions of yaws but as Turner says Hallenberger s own study does not bear this out

Vitiligo associated with atrophy and dyschromia of the skin is found in widely scattered parts of the world not only in pinta but also in syphilis yaws bejel and other examples of treponematosis It is one of the late hallmarks of the juvenile untreated type of infection and apparently is due to loss of pigment and atrophy of the skin associated with perivascular infiltration and thickening of the intima to the point where normal nutrition of the dermal tissues can no longer be main tained

In regard to the pathology of the bones in yaws and syphilis Williams[13] says that in yaws there are 1) areas of absorption which look like congenital syphilitic bones 2) the same with the addition of new bone formation and 3) thickening of subperiosteal bone tissue The latter two he says are especially like syphilis All

three have been demonstrated in roentgenographic pictures of bones in juvenile syphilis (bejel)[107]

Weller[1 8], after a study of 169 aortas from a Haitian population with a high incidence of yaws scars and yaws history but also including numerous patients with a genital scar and history of syphilis, demonstrated treponemes in 30 per cent of the cases with positive tissue lesions Sixty five and seven tenths per cent of the cases showed histologic il lesions which in temperate zones are attributed to syphilis In a later series of visceral infections with treponematosis (yaws or syphilis) he again found[1 9] the same common picture and confessed his inability to match the original diagnosis with the subsequent histopathology He concludes One of the three conditions must exist either yaws and syphilis are essentially the same disease or the group of patients here considered has such a high incidence of syphilis that the evidences of this disease are overwhelmingly obtrusive or yaws and syphilis if different diseases, produce identical aortic (and visceral) lesions, adding still another item to the list of indistinguishable attributes to the two conditions "

Ferris and Turner[35] in a recent (1937) study of the comparative histology of yaws and syphilis in Jamaica find no basis for the concept of epidermotropism They give the coup de grace to the histological differentiation of the two conditions stating that all the histological features of yaws lesions can be duplicated in one or other of the lesions of syphilis and failing to find any feature which may be singled out as a criterion They name 11 features common to the two forms of treponematosis 1) acanthosis 2) perivascular infiltration of lymphocytes and plasma cells 3) giant cells, 4) swelling of the capillary endothelium 5) distribution of the spirochetes 6) epithelial hyperplasia 7) proliferation of fibroblasts, 8) presence of caseous necrosis, 9) depth of cellular infiltrations, 10) predominance of plasma cells and 11) morphology of *T pallidum* and *T pertenue* in the tissues ' Finally they say ' the histologic feature which has been stressed as characteristic of syphilis is sclerosis with endothelial hyperplasia of blood vessels If we accept this criterion, we should discard all of our secondary syphilitic lesions because they do not fulfill this requirement On the other hand, all of our late ulcerative lesions of yaws would be diagnosed as syphilis because some degree of vascular change is present in all Strong and Shattuck, however admit that all syphilitic lesions do not show typical modifications of blood vessels and especially in the tertiary stages syphilitic lesions cannot be distinguished from those of yaws by their histologic appearance In conclusion Ferris and Turner state ' histological criteria for the differentiation of the cutaneous and subcutaneous lesions of yaws and syphilis are in general unreliable [5]

Cross immunity between yaws and syphilis is another of those abandoned redoubts in yesterday s field Experiments were made which on their face seemed

to show that yaws and syphilis could run concurrently in the same individual, and this was adduced as final proof that the two infections were altogether different Subsequent studies however in the immunity of treponematous infection have shown fallacies in the methods and the conclusions of these earlier experiments Even Fox[8] today says there is eventually complete cross immunity between yaws and syphilis and cites as illustration his belief that the natives in Guam have no syphilis because they all had yaws in childhood

The best controlled and analyzed data on this subject were collected recently by Turner[1] in Jamaica Reviewing the previous artificial transmissions of Thomson Maxwell Paulet Charlouis Sellards and Lacy and Schobl he points out that in the main they have demonstrated that autoinoculation in yaws has yielded negative results while patients with yaws of fairly short duration have been susceptible to the inoculation of heterologous virus (i e from another individual) Failure to develop a lesion can be accepted as indication of acquired immunity

Turner presents 3 groups of patients 18 were reinoculated with their own (i e homologous) strains of *T pertenue* 67 with heterologous strains and lastly 10 persons with syphilis were inoculated with active yaws virus The results of the autoinoculation of the 18 yaws patients indicated that resistance to such reinfection in yaws develops early and obtains throughout the time that lesions are present The results of heterologous inoculation of the 67 yaws patients indicated that immunity to such strains varies directly with the length of time since the original infection and often several years elapse before such patients are refractory to a second inoculation In other words immunity to one s own organism begins quite early in the course of yaws but it may take several years time to attain enough immunity to be refractory to an organism originating in one s neighbor

Turner breaks down his group of 67 patients into 3 subgroups 26 with active lesions of yaws 23 that were latent because of treatment and 18 who had been pontaneously latent for longer than years Of the 18 pontaneously latent cases only 16 7 per cent were susceptible to heterologous reinoculation Of the 26 with active lesions 42 3 per cent were susceptible and of the 23 that were latent because of treatment 82 6 per cent were susceptible These results are of prime interest they suggest as Turner says that the development of immunity is retarded by treatment which interrupts the normal course of disease

Comparing his work with that of earlier experimenters Turner points out that Charlouis and others who inoculated yaws patients with syphilis virus and vice versa and secured concurrent infections really made these reinoculations during the stage when their patients would not yet be immune to any heterologous treponeme Any differential inference is therefore lost

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Kenneth McLeod said when the micro organisms causing syphilis and frambesia were discovered and found to be identical or distinct the question raised by Mr Hutchinson would be finally settled but meantime the issue presented by him must remain very debatable

This interchange is quoted here because it shows that after almost 50 years and almost acres of pages the situation is still about where it was in the first year of this century McLeod seemed to believe that if the organisms were found to be identical the question would be finally settled But though everybody agreed the treponemes when found were indistinguishable that did not settle it Then the serological tests were developed but again hopes for a differentiation were dashed Differences in symptomatology have been shown to be due to environmental circumstances and to consist of degree rather than essence The same is true of histopathology and cross immunity And so we approach the mid mark of the century still awaiting the criterion so long sought for by those who are convinced that yaws and syphilis are distinct diseases So many people have taken this position that the search must go on for the proof to support the position Thus far the objective has been an ignis fatuus The party which has been most numerous and the most dogmatic that the argument is over and settled in favor of the separation of yaws from syphilis, has been the most indefatigable in further efforts to prove the point because positions once confidently held have had to be abandoned one after the other In 1944 Fox's[41] differential list has shrunk one may check the items in search of one that is truly of differential significance

Yaws	Is nonvenereal	No significance
	No eruption on mucosae	No significance
	No intrauterine infection	No significance
	No roseola	No significance
	Differences in primary and secondary	No significance
	Slight involvement of vital organs	No significance
	Histopathological differences	No significance
	Different response to animal inoculation	??

The first 7 points concern the infection in man It will be seen that no differential criterion has been found in man which will stand up to critical examination It remains therefore to see whether some differences may be found in animals to support these arguments concerning this human disease arguments which have failed to find adequate support in man himself The embarrassing nature of this predicament is obvious The situation is somewhat as follows In order that it be finally settled that yaws and syphilis are different diseases rather than patterns of the same disease it will be necessary to prove that *T pertenue* is demonstrably different in some respect from *T pallidum* instead of being as it

Jahnel and Lange and Van der Schaar, whom he cites, inoculated neuro syphilitic patients with yaws and got equivocal results, showing that these late forms of syphilis exhibit resistance to yaws far greater than that displayed by normal persons Turner had a group of 10 syphilitic patients who had acquired the infection at least several years before None of these showed any result from inoculation with yaws virus That there was no doubt of the potency of the virus is shown by the facts that of 10 persons with yaws of more than 10 years' duration, who were inoculated with the same virus, 2 showed lesions, while of 10 persons with yaws of less than 3 years duration 9 gave a positive result

Turner in discussing these results says ' Persons with yaws may frequently go successively through stages in which according to the degree of immunity present reinoculation would conceivably be followed, respectively, by 1) an attack of yaws resembling the first attack 2) an abortive attack, 3) superinfection without clinical lesions and 4) no infection from the second inoculation' Chesney, he says, has evidence indicating that, while immunity in syphilis is a product of the stimulus of active lesions, once established it is perpetuated in the absence of manifest lesions and even in the absence of infection It is probable that most people would begin Turner's next sentence with the word doubtless ' Possibly ", he says ' this concept of the nature of immunity in syphilis may apply in large measure to yaws also '

In conclusion, Turner says Syphilis confers an immunity to yaws which is as great as, if not greater than, that conferred by yaws itself "

Species or Strains?

The place was London and the date Sept 1, 1900, the occasion was a medical meeting and the subject yaws The British Medical Journal[73] reported three speakers as follows

" Mr Hutchinson stated his firm conviction that yaws was syphilis modified by race and climate He considered that syphilis found its way into this country not from America but from the African coast In fact when traffic commenced between the West African Coast and Western Europe, syphilis appeared Why yaws was not seen in England was because any European who contracted the disease in the tropics came back with syphilitic signs and symptoms Sibbens in Scotland and the frambesia that occurred in Cromwell s army in Scotland were no doubt examples of local outbreaks of yaws that was syphilis misnamed or neglected

" Sir Patrick Manson said yaws like many parasitic diseases peculiar to the tropics, could not be imported to colder climates owing to the death of the parasite on account of the absence of a continued high temperature

of the interpretation of data Stokes[4] says *The interplay between host and* organisms in syphilis is evidently an extremely complex affair It is unusually difficult to study it in man because it is rarely possible to control more than two factors namely the strain of the organism and the duration of the infection or time element in any group of comparable cases The commonest example infection of *the husband and wife with the same organism is weakened by the adventitious* factor of sex by passage through an intermediate host usually the husband before reaching the wife and by variations of behavior of infection dependent on the site of the inoculation If Stokes is so cautious in evaluation of the relatively simple matter of conjugal syphilis how much more caution is required in the evaluation of results obtained by the injection of rabbits with virus from a skin papule of juvenile treponematosis in Jamaica and from a venereal primary lesion of an adult in Baltimore?

The preceding complexities however are simplicity itself compared with the fourth point If one could count on *Treponema pallidum* remaining as an unchangeable point or baseline one might then hope to bring *T pertenue* into sufficient orientation with it to get an approximate idea of their biological relationship But *T pallidum* itself is far from being a fixed point it is notorious for its ability to change its characteristics to meet changing conditions Pearce [9] for example says it is possible to develop strains of various sorts in rabbits by varying the time and place of inoculation and by manipulation of a multitude of environmental factors The character of disease from a given strain varies with the sex of the experimental animal with the season and even with the year Infections are particularly mild in summer and severe in spring and fall Beerman[4] says recent studies seem to indicate possible adaptability of the treponeme to certain organs Stokes[11] says the practically unvarying asymptomatic infection in the mouse has provided the means to modify the characteristics of the organism with respect to tropism for such structures as the nervous system Thus says Beerman they may acquire an especial virulence for the central nervous system when they have lived as saprophytes in nervous tissue for a long time Kolle and Schlossberger have shown that differences in virulence make it possible to superinfect animals which are carriers of weaker strains by inoculation with stronger strains Stokes[1] says animal experimentation has emphasized the influence of the site of inoculation

Yet these strains are not fixed Beerman quotes Naegeli s reference to the labile character of the treponeme He says the behavior of a given strain is by no means constant Pearce says the evidence of animal experimentation is against fixed biological strains in spirochetes Strains of spirochetes from man differ in their virulence in respect to inoculated animals[4] The parasites also behave very differently in different experimental animals apes react with three

has been, just the name for the treponeme that causes yaws Therefore, say those who believe that *T pertenue* is a different species, we will put treponemes from yaws cases into rabbits and put treponemes from syphilis cases into other rabbits, and we will see the results in the two groups of rabbits If results are the same, the question still may be kept open If the results are not the same, this differerce in rabbits will constitute proof of the essential nature of the difference between the two human diseases This is called the biological test Its purpose surely is not for the diagnosis of borderline clinical cases, it is obviously too unwieldy for this No one would hold up a diagnosis until rabbits had been inoculated to see if they had indurated testicles or a granular periorchitis Its rationale apparently lies in the hope that it will prove that there exists such a species as *T pertenue*, because a parasitic disease without a specific cause is in a bad way

Before proceeding to a review of the experimental work in this field it is necessary to make some general observations In the first place, everyone will agree that conclusions about a human disease drawn from observations made after its transfer to animals must be treated always with conservatism Secondly, the selection of material for the injections is subject to some scientific scrutiny If such material could be standardized and if one could draw from a ' yaws vial ' and from a ' syphilis vial ", one could feel less insecure but no spirochete bears an identification tag The experiment is started with two treponemes which can not to be distinguished by any known means The experimenter is therefore, thrown back on " clinical differentiation " But here again, this is something which in the course of time has proved impossible That the current experiment is necessary is definite proof that clinical differentiation has failed to differentiate

Be that as it may, the experimenter goes for his yaws spirochetes to a locale where yaws exists and draws serum from a typical yaws lesion in a patient with a typical yaws history Incidentally, the serum contains other organisms than spirochetes but these cannot be excluded because culture of the spirochete is out of the question Similarly syphilis spirochetes are taken from a patient in a venereal disease clinic with a typical genital lesion acquired with a typical history of venereal exposure

If there results a difference in the rabbits, the evaluation of that difference is going to be difficult and this is the third point How is one to know whether an " inherent biological difference ' even if found is due to fundamental specific difference between the two parasites or due to the fact that in the one case the treponeme is the descendant of countless generations of treponemes, which have lived unrestricted lives under the influence of childhood immunological reactions and that in the other case the treponeme has a chain of progenitors which have been subject to various forms of treatment and have eked out an exiguous existence under the influence of adult immunological reactions? As to this matter

of the interpretation of data Stokes[4] says The interplay between host and organisms in syphilis is evidently an extremely complex affair It is unusually difficult to study it in man because it is rarely possible to control more than two factors namely the strain of the organism and the duration of the infection or time element in any group of comparable cases The commonest example infection of the husband and wife with the same organism is weakened by the adventitious factor of sex by passage through an intermediate host usually the husband before reaching the wife and by variations of behavior of infection dependent on the site of the inoculation If Stokes is so cautious in evaluation of the relatively simple matter of conjugal syphilis how much more caution is required in the evaluation of results obtained by the injection of rabbits with virus *from a skin papule of* juvenile treponematosis in Jamaica and from a venereal primary lesion of an adult in Baltimore?

The preceding complexities however are simplicity itself compared with the fourth point If one could count on *Treponema pallidum* remaining as an unchangeable point or baseline one might then hope to bring *T pertenue* into sufficient orientation with it to get an approximate idea of their biological relationship But *T pallidum* itself is far from being a fixed point it is notorious for its ability *to change* its characteristics to meet changing conditions Pearce for example says it is possible to develop strains of various sorts in rabbits by varying the time and place of inoculation and by manipulation of *a multitude of environmental* factors The character of disease from a given strain varies with the sex of the experimental animal with the season and even with the year *Infections are particularly* mild in summer and severe in spring and fall Beerman[4] says recent studies seem to indicate possible adaptability of the treponeme to certain organs Stokes[117] says *the practically* unvarying asymptomatic infection in the mouse has provided the means to modify the characteristics of the organism with respect to tropism for such structures as the nervous *system* Thus says Beerman[4] they may acquire an especial virulence for the central nervous system *when they have lived as saprophytes in nervous tissue for a long time* Kolle and Schlossberger have shown that differences in virulence make it possible to superinfect animals which are carriers of weaker strains by inoculation with stronger strains Stokes[1] says animal experimentation has emphasized the influence of the site of inoculation

Yet these strains are not fixed Beerman quotes Naegeli s *reference to the* labile character of the treponeme He says the behavior of a given strain is by no means constant Pearce says the evidence of animal experimentation is against fixed biological strains in spirochetes Strains of spirochetes from man differ in their virulence in respect to inoculated animals[4] The parasites also behave very differently in different experimental animals apes react with three

stages like man, rabbits begin like man but stop after about four months, and mice are infectious but never give any signs[10]

Bessemans gives specific illustrations of treponemal functional variation A temperature of 40° C for 2 hours or 42° C for 1 hour kills treponemes in a rabbit testicular syphiloma, whereas it requires temperatures above 46° C to kill spirochetes in a popliteal lymph node Node treponemes retain mobility and virulence longer in vitro than testicular treponemes It takes 2 500 treponemes from testicles to infect another rabbit but only 3 to 13 from nodes In other words there is marked contrast in the "specific infectious threshold Levaditi showed that he could not infect lymph nodes directly by injection of syphiloma treponemes that is the lymphatic system is an unfavorable environment for their growth The brain substance of paretics is not infectious for rabbits whether or not it contains motile live treponemes These treponemes have either atrophied (virulence permanently reduced) or adapted themselves (virulence temporarily weakened) We therefore share with Foster the opinion that the treponemes occurring in the brain of paretics constitute a variety which has become so accustomed to its habitat in the central nervous system of man that it has lost its pathogenicity for animals ' [8]

Bessemans adduces other examples of physiological variation, 1) the progressive development of the resistance of the parasite against the immune bodies of the host 2) its difficult adjustment toward life in vitro and after this has occurred its absolute loss of virulence 3) variations of *T pallidum* produce definite types of predominating lesions, 4) increased resistance to drugs, 5) increase in virulence following repeated passage through animals and 6) differing respons of strains to horse serum Bessemans reports that comparatively few treponemes are necessary to produce a syphilitic infection in a new rabbit when taken during the incubation period but many are required to obtain the same result after the syphiloma has evolved In the clinical field he thinks the difference in character between medieval and modern syphilis may betoken a functional change in the treponeme

In contrast to these examples of functional variation Bessemans finds the morphology of *T pallidum* always the same within relatively narrow bounds of length thickness and number of coils Treponemes tend to thicken and lengthen in culture and to become shorter and thinner in vivo when they are more motile (and more virulent) He concludes that 'from all this it is apparent that *T pallidum* is a changeable micro organism With a change of habitat it changes its functional properties but it does not change its form Sometimes its function is permanently modified more often it can revert to its former life habits The organism causing syphilis is a morphological unity, but functionally it has innumerable aspects

Treatment resistant strains have been observed in humans but their resistance was lost when they were transferred to rabbits Beerman[4] for the first time has isolated a resistant strain which retained this characteristic after transfer In his experiment 5 of 23 rabbits given more than a curative dose were not cured ' He believes this demonstrates intrinsic refractoriness toward the arsenicals This quality he says tends to be lost but still appeared strongly in a case of 8th passage This strain had a tendency to produce asymptomatic experimental infections and inconspicuous low grade tissue reactions with tendency to rapid spontaneous involution

From these scattered observations one is persuaded that *T pallidum* is an extraordinarily nimble parasite with an uncanny power of adaptation and further equally important that it retains the power of reversion to a former state when conditions are reversed Stokes [7] speaks of the extraordinary adaptation of *Spirocheta pallida* to its life in man An organism which in nature affects no other species and which in the vast majority of cases is able to maintain its foothold in tissue literally through decades of symptomless infectivity meeting a wide range of growth conditions and therapeutic opposition with an almost unbelievable ability to survive every test is easily one of the sovereign instances of parasitic adaptation in the entire field of disease It must therefore be a matter of great concern to the man who sets out to establish the biological relationship of the treponemes of yaws and syphilis by their respective reactions in rabbit testicles to remember that his yardstick which must be *T pallidum* is itself subject to such a high degree of functional variability

However the list of difficulties which the experimental biologist must face is not yet exhausted Two remain more nearly crucial than any of the preceding If *T pertenue* belongs in taxonomy in a coordinate position beside *T pallidum* the difference in the yaws rabbits must be of such an order of magnitude as to constitute it a separate species worthy of bearing its specific name and secondly the difference must be so constant that there is never any dubiety It must be a real criterion clear definite and constant These two points will be examined in detail

Taxonomy is built upon morphology Even in unicellular organisms of simple structure this is the accepted rule Objection may be made that it is possible that the limits of human vision are failing to recognize morphological differences which are there to be seen if they could be seen but this is getting metaphysical Manwell speaking of speciation in the plasmodia says a species should have definite and more or less unique morphological characters and it should not hybridize i e it should breed true Recapitulation of the history of treponematosis since the Proto negroid migrations shows a constant shifting going on simultaneously in all parts of the world between the juvenile pattern and the adult venereal pattern usually from the yaws to the syphilis type but sometimes in the reverse direc

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The most comprehensive and best controlled report on the comparative behavior of yaws and syphilis treponemes in experimental animals is given in a series of papers by Turner and coworkers In 1932 Turner and Chambers[1] came to the conclusion that the rabbit is a better experimental animal than the monkey for the transfer of yaws spirochetes from man to animal and that only testicular inoculation of the rabbit yields satisfactory results In 1934 Turner and Chesney [1 3] found certain differences between the two experimental infections and had the following comment to make

We do not wish to give the impression that every rabbit in this series inoculated intratesticularly with yaws virus exhibited lesions that were distinct from all those that occur in animals inoculated with *T pallidum* for an occasional yaws rabbit will present a testicular nodule which because of its size and induration cannot be distinguished from nodules observed in experimental syphilis These instances are the exception however and we have been struck by the differences in the character and evolution of the lesions caused by the two organisms in the vast majority of rabbits It is difficult to escape the conclusion that the differences observed in the two experimental infections were to be ascribed to inherent differences in the strains of treponemes themselves This conclusion if true lends support to the view that at the present time syphilis and yaws are different diseases and that yaws is not just syphilis modified in some mysterious fashion by circumstances which operate in the tropics It is of course entirely possible that at some remote date in the past the treponemes of yaws and those of syphilis were identical and that they produced only one type of disease but of this there is no definite evidence at the present time There also exists the possibility that the yaws strain of treponemes may in the course of time and as the result of animal passage change their characteristics in such a way that the disease produced by them in rabbits may become similar to that produced by strains of treponemes obtained from syphilis As yet we have not seen any evidence that that event is likely to happen In a footnote at the end of the article the authors refer to a recent report by Manteufel on a similar series of comparative experiments He noted a gradual change in the experimental yaws lesions in the direction of syphilitic characteristics so that the distinction was eventually lost

The preceding quotation calls for the following comment It will be granted that these careful workers have met the first four difficulties as satisfactorily as is humanly possible As a result of their experiments they have established in most of their rabbits definite differences related to strains of yaws treponemes and strains of syphilis treponemes Now the vital question is are these observed differences of sufficient magnitude clarity and constancy to constitute grounds for assuming that each represents a species? If the answer is affirmative the yaws treponemes are entitled to the specific name of *T pertenue* and insofar as animal

tion Hutchinson said he could not see why, if yaws and syphilis were not the same disease, they could not exist side by side in the same race and under the same conditions of life, which they never have done except during periods of transition

This approach therefore, has not thrown light on the speciation of the treponemes since there is no difference in their morphology, and the indications are that they do not breed true Taking another approach suppose the two treponemata are said not to have specific morphological differences but to have specific physiological differences This of course is not the usual disposition of physiological differences which are preferably attributed to strains rather than species From the evolutionary standpoint physiological variation occurs long before morphological variation it is smaller in magnitude, less fixed and more subject to internal and external influences Strains of spirochetes, all can accept At what point does a physiological strain become so differentiated from its fellows that it becomes a species? And can one be sure that the postulated "physiological species has become fixed and is not liable to slip back into the old groove, when conditions change? These are important questions They have to be answered in precise terms before the species can be accepted For the strain is by definition flexible, the species by definition rigid It is not necessary to define a strain, but it is obligatory to define a species This truth has been utterly neglected in the case of "*T pertenue*' this is a species which no one has ever defined, and no one has the right to give a scientific name to something which he cannot define The same gravamen can be brought against *T carateum* the treponeme associated with pinta An attempt to define it ends up in a description identical with *T pallidum* Let no one at this point say he would define *T pertenue* or *T carateum* in terms of the clinical pictures they cause It is precisely because a definition of that kind has proved impossible that the experimental biologist is to attempt differentiation by rabbit inoculation The literature is full of writers, who are satisfied that yaws and syphilis are different because they are caused by different species of treponemata and of those who are equally satisfied that *T pallidum* and *T pertenue* are different, because they produce different clinical pictures

That is the fifth difficulty faced by the biologist if he is to establish *T pertenue* as a distinct species its difference from *T pallidum* must be of the order of magnitude of inter species differences elsewhere in the unicellular phylum The sixth point is that the difference must be universal and constant There must be no failure to find it in any part of the world or failure to find it at any given time in any given subject There must be no straddling, no shifting of the dividing line no intermediate forms no disregarding of exceptions no difference between this year and last year no borderline cases no approximations no 'vast majorities' It will have to be recalled that a specific differential that fails to differentiate in 5 per cent of cases has lost 95 per cent of its differential value

overlap and shade into each other A review of his experiments shows exceptions to every statement True that the majority in each case were different but one can not prove speciation by majorities What is required is one point which is true of all syphilitic rabbits and not true of any yaws rabbits The most significant rabbits in his yaws series were the 3 in which the lesion was quite like that produced by syphilis the 1 yaws rabbit in 97 which had generalized lesions and the 2 whose nodes were infectious to normal rabbits these were the important ones because they invalidated the criterion Suppose for example Turner were given an unknown treponeme to determine whether it were *T pallidum* or *T pertenue* Could he by application of this experimental method determine which it was? He could not he could make a good guess on the law of chance and probability *but precise differentiation — No The matter is still bedeviled by* the lack of an exact qualitative difference between the two treponemes As long as their differences are in degree and not in essence they have to be considered strains of the same species

The claim may be made that yaws and syphilis are different diseases caused by strains of the same parasite but this position is dangerous For strains are fluid concepts especially in such a flexible parasite as *T pallidum* and if strains can overlap and run into each other then the diseases they cause must do so also and what becomes of the differential diagnosis then? Hewer (personal communication) has stated We shall probably find many different actual strains of spirochete from every gradation between European syphilis and yaws and also many different races of people who react in their own way to all strains! I am quite sure it is not a neurotropic strain that is responsible for general paralysis of the insane and I very much doubt whether the yaws strain is only capable of producing yaws There is pretty good evidence from animal work at any rate for the existence of different strains but whether one is justified in arguing from that a definite causal relationship between the identity of the strain and the type of lesion produced in man is surely very doubtful So even if one succeed in establishing strains of yaws and syphilis which produce constantly different lesions in monkeys one will not feel sure that the diseases are really different

Williams [8] rather cautiously approaches the same concept He says Probably all will agree that the spirochetes of yaws and syphilis originally had the same spirochete *for an ancestor The evidence that is available gives me the impression* that the spirochete of yaws or syphilis has undergone a functional but not a morphological mutation in some human host giving rise to the other infection and that the resemblances between the two infections indicate that the new infection has evolved from the older one in comparatively recent times He is not willing to take a step further and admit that a reversal of circumstances might produce a reversal in these functional characters of the spirochete Hutchinson is as usual

experimentation goes yaws is a disease sui generis due to infection with a specific parasite If the answer is negative, the yaws treponemes are not entitled to a specific name they represent strains of *T pallidum*, yaws is not a disease sui generis, and the two clinical conditions, yaws and syphilis, represent phases or patterns of one disease, treponematosis Without passing judgment at this point upon the magnitude, clarity and constancy of the differences, one can at least say that on the basis of the experiments and conclusions cited above the speciation of *T pertenue* is not proven

Turner returned to the problem with a second series of experiments in 1937[1] He noted distinguishing features between the two strains from the first passage In experimental yaws there were ' multiple small granules within the body as on the surface of the testis or epididymis without enlargement or induration of the testis In experimental syphilis there was an " initial lesion uniformly characterized by the presence of a large indurated lesion within the body of the testis " Previous observers have described granular periorchitis as characteristic of yaws Fifty five of Turner s 191 yaws rabbits showed this One hundred and eighty five showed lesions ' characteristic of yaws ', 3 were ' mixed ' and in 3 ' the lesion was quite like that produced by syphilis " In Turner s 102 syphilitic rabbits all had marked testicular induration ' In no instance did the testicular lesion resemble that described for yaws " There were generalized lesions in 1 of 97 yaws rabbits and in 42 2 per cent of the syphilitic rabbits There were metastatic lesions (from one testis to the other) in 62 5 per cent of the syphilis rabbits and in 13 2 per cent of the yaws rabbits

As to the incubation period in the 2 groups of rabbits the majority in both fell between 21 and 42 days but in yaws 10 per cent were less than 21 days and 33 3 per cent were more than 42 days, whereas in syphilis 30 per cent were less than 21 days and 5 6 per cent were more than 42 days In subsequent passages the incubation period in yaws tended to shorten and the extent of the initial lesion tended to increase whereas there was no change in the syphilis rabbits When lymph nodes were transferred from infected rabbits, 7 of 10 nodes from syphilis rabbits were infectious for normal rabbits and 2 of 9 nodes from yaws rabbits

Everyone will agree with Turner in the following statement if he will insert one word, usually The conclusion seems justified therefore, that the spirochetes causing the typical manifestations of yaws in Jamaican Negroes (" usually ') produce a different disease picture in rabbits from that produced by the spirochetes obtained from Jamaican Negroes presenting the classical picture of early syphilis How long such differences would continue to be manifest cannot of course be predicted He says they persisted for a number of animal passages over a period of several years '

The flaw in Turner s deduction is that the two disease pictures ' in rabbits

parasitic disease it represents the activity of a parasite definitely distinguishable from other parasites This is a picture of treponematosis caused by *T pallidum*

A distinction must be made between a disease entity and a clinical entity The latter is a syndrome or clinical pattern a group of signs and symptoms which *may occur together A clinical entity lacks the quality of stability depending for* its existence upon extraneous factors Temporarily there may be transitional entities as one shades into another under changed conditions The syndrome is fundamentally fluid in character remaining an entity only so long as the forces that originally produced it remain in operation Examples of clinical entities are yaws venereal syphilis pinta and other patterns of treponematosis Clinical entities are separated from each other by differences of a smaller order of magnitude than disease entities They may be produced for example by different strains of the same species one may show fewer lesions of the mucosae than others another may show disproportionate disturbance of the pigmentation of the skin one owing to the habits of certain people may be a childhood infection while another syndrome is transmitted venereally in adults It is important to note the size of the differences between two clinical entities such as yaws and syphilis compared to the size of the differences between two disease entities such as treponematosis and leptospirosis for example

From the standpoint of precision it has been unfortunate that the dichotomy in treponematosis between the venereal and nonvenereal patterns has been so obtrusive clinically and so convenient for purposes of discussion that the medical profession has come to regard them as different diseases instead of different clinical entities Turner has expressed this point of view He says It is quite practicable for the purpose of discussion to group such reactions according to the degree with which they resemble each other The number of groups and subgroups thus formed need be limited only by their usefulness For over 200 years sufficient differences between (yaws and syphilis) have been noted to make it useful to designate them by different names Yet surely convenience is not a legitimate basis for the classification of diseases One never knows where the application of such a principle will lead There would be no objection of course to retention of the different names provided they were recognized as patterns of the same disease but this apparently is not Turner s meaning

Two other words now require definition *Epidemiology* is narrowly defined as the science of epidemics but it will be used here in the much wider sense to include the sum total of environmental influences involved in a given disease It is used in distinction to *etiology* which represents the causative agent In every infectious disease there are three factors the host the parasite and the environment The final picture of the disease in a given locale depends on the interaction of these three factors They are like the three apices of an isosceles triangle whose

forthright He says[74], It may perhaps prove to be a fact that the spirochete bred in different climates and in different races is capable of some modifications These modifications may no more constitute specific characters than do the horns of a Scotch sheep or the hornless dusky face of a wellbred Southdown "

The position at the end of this section is, therefore, the following Search for a diagnostic criterion between syphilis and yaws in man has been fruitless the admitted differences have always proved on analysis, to be quantitative in nature

Search for a diagnostic criterion between syphilis and yaws in the rabbit was then undertaken Differences, as was to be anticipated, were found but these differences were of the order of magnitude of strains, and they showed strain characteristics of fluidity and lack of universality In short, they were not differences of the magnitude the constancy, the clarity and the uniqueness associated with species

Therefore evidence both in man and rabbit favors the concept that the treponemes of syphilis and yaws are strains of the same organism, Genus *Treponema* Species *pallidum* Retention of '*T pertenue*', which has always been a straw species is not justified

If yaws and syphilis are caused by strains of the same species they are varieties of the same disease The law of parsimony in diagnosis would not permit of two diseases caused by the same species of parasite The proper etiological name of the disease is treponematosis The venereal variety is syphilis the juvenile variety is yaws frambesia or pian Syphilis is not yaws neither is yaws syphilis, both are treponematosis each is a pattern of treponematosis

Yaws and syphilis are so different from each other in their respective habitats that laymen distinguish them without difficulty If they are patterns of the same disease whence arose these clinical differences? Whence arose the biological differences between the strains of *T pallidum?* Have the clinical and biological differences any relationship? The succeeding section will discuss these questions

Epidemiology

Before proceeding to a discussion of the role of epidemiology in treponematosis it will be necessary to define some of the terms in common use A *disease* is a definite morbid process having a characteristic train of symptoms An *entity* is an independently existing thing When the expression 'disease entity', is used, the independent or unique quality of the disease concept is emphasized Its character has the quality of stability its course is definitely predictable its pathology remains true to certain fundamental tissue changes its serology and immunology follow definite laws its therapy is consistently effective In the case of a

from B because A appears first as a sore on the genitalia and B appears first as a skin eruption The respective sites of those first lesions are due to environ mental influence In A the sore is due to sexual contact between mucous sur faces in B to skin contact of two children one with skin sores and one with a scratch from tall grasses Similarly let no one say A is a different disease from B because it is transmitted through mother to child and B is not for B is acquired in childhood and this epidemiological fact accounts for lack of such transmission In fact, A when similarly acquired in childhood also fails to be transmitted Let no one assert that A is a different disease from B because there are strain dif ferences in their respective parasites when injected into rabbit testicles Func tional variations of this degree of magnitude in treponemal strains are explicable on the ground of habitual environmental influence e g strain Y propagating itself in children strain S in adults Y introduced through general skin surfaces S through the skin of the genitals Y affecting the majority of the population S af fecting a small segment Y passing through host after host untreated S subjected to various forms of local and general treatment strain Y manifesting itself with a florid skin eruption strain S seldom allowed to proceed through the normal evolution of the infection The experimental biologist who can produce strains of treponemes at will by varying the environmental factors should be particularly hesitant to ascribe inherent biological characteristics to the treponemes of yaws and syphilis especially if by this he implies that these characteristics are permanently established The evidence of his own work is that these differences are linked with environmental influences and will vary with them

It is particularly true of treponematosis that epidemiological influences de termine the pattern of the disease in a given locale but every infectious disease shows this phenomenon to some degree For example it is fully demonstrated that such diseases as cholera typhus dysentery and typhoid are limited not by geography but by sanitation If treponematosis like these diseases had only one epidemiological pattern the yaws phase sanitation could wipe out trepone matosis as effectively as it has done cholera The peculiarity of treponematosis is that it has an alternative epidemiological pattern which can persist in spite of rigorous sanitation Environmental conditions which make yaws impossible are just those which make venereal syphilis possible The view generally held favors the assumption that yaws is abolished by sanitation and that syphilis which appeared on the earth as a new disease now encroaches on yaws territory as the latter recedes For example Connolly in Kenya says I am of the opinion that yaws is giving way slowly to syphilis and after all as the cleanliness and general condition of the natives improve yaws should tend to disappear naturally [8] The interpretation expounded herein however is that venereal syphilis is the logical evolutionary outgrowth of the primitive yaws pat

sides represent lines of force acting in both directions Each of the factors influences to some degree both of the other factors Changes in the host may occur, such as the development of racial immunity or the effects of unrecognized vaccination intercurrent infections and diseases, wars, food deficiencies, the stress of life, changes in the parasite may result from mutation, variation and adaptation changes in environment arise from man's purposeful manipulation of his surroundings and his own habits The final result of the mutual influence of the three factors may be a number of clinical entities, depending upon the respective strengths of the three forces, but the triangle remains the disease entity As Rolleston[106] says Changes in clinical characters of disease are interesting not only to those of us who from the passage of time have watched once familiar maladies alter their features and become rare, and have seen new ones come on the scene but to every one because different years often show differences in the occurrence or the prominence of certain characters and manifestations of the common epidemic diseases It would indeed be strange if diseases always remained the same ' In the case of treponematosis, man is the host *T pallidum* is the parasite, and the environment is composed of a multitude of influences such as temperature humidity, the presence of insects and vegetation, trauma altitude and even geology Obviously out of such an unstable field of force will come a host varying considerably in his manner of reaction toward the infection and a parasite varying considerably in the direction of functional strains but these variations remain within the framework of the disease Tuberculosis may be predominantly either a disease of the lungs, of the lymph nodes or of the bones, depending somewhat on the age of the patient through what route the infection was acquired and innumerable other factors Scrofula and phthisis, which used to differentiate two of these forms, have fallen into disu e the inclusive etiological term tuberculosis being preferred Plague displays two distinct syndromes, depending on epidemiological factors we call one bubonic and the other pneumonic They are two patterns of the same disease, both caused by *Pasteurella pestis* They do not look alike, but no one has proposed naming their respective causes ' *P inguinalis* and *P pulmonalis* ' in spite of possible functional variation because their differences trace back to the ' how ' and ' where " of the disease, in other words its environment No one would think of classifying pulmonary tuberculosis and pulmonary plague together though there is superficial resemblance in their clinical patterns the cough, the expectoration the air borne bacilli They are differentiated because their etiological agents have distinct characters

These illustrations point to the truth that classification must be based upon etiology epidemiology is very influential in determining the appearance of a disease, and sometimes can play strange tricks however, with regard to diagnosis it is a siren leading into dangerous waters Let no one say A is a different disease

climate In general there was correspondence between the prevalence of this fly and the incidence of yaws though yaws was absent in some places where *H pallipes* was numerous The authors conclude Yaws has a widespread, patchy distribution in rural Jamaica Where it is common there are practically always found a heavy rainfall, fertile moisture holding soil supporting an abundant vegetation a peasant population living under insanitary conditions and many *H pallipes* flies

Turner and Saunders in 1935[1] [4] stated that in Jamaica over 90 per cent of affected persons acquired yaws before the age of 15 years a fact which as they say clearly indicates in itself the nonvenereal character of the disease Over 90 per cent of the infectious cases were under 20 years Landowners and whites they observed do not get yaws since by their manner of life during the most susceptible age there is no contact with people having yaws

As to attack rates they were found to be much lower in adults than in children In one series the attack rate for those under 20 was 135 per 1 000 whereas it was only 10 per 1 000 for those over 20 In other similar series the relation was as 103 to 5 64 to 2 and 62 to 0 Adults who moved into the district after the age of 20 showed an attack rate of 13 The highest attack rate was during the school age notably between 10 and 14 years[1] This is statistical confirmation for the observation that there is something in the epidemiological pattern of yaws which makes the juvenile comp nent of the population particularly susceptible to the infection

The literature on the epidemiology of treponematosis is of course enormous The preceding extracts are given as illustrations of the direct influence of climatic and social factors on the pattern of disease Before this section closes however the views of Turner [1] on this subject will be examined for he rejects the idea that such factors as race age portal of infection and mode of life play an influential role in determining the character of the disease picture Turner takes this unusual view because he is impressed with the functional differences between the treponemal strains of yaws and syphilis in experimental animals It is well to note by the way that Turner refers to yaws as a clinico epidemiologic syndrome he speaks of the syndromes yaws and syphilis and although he mentions *T pertenue* he continually refers to strains rather than species of trep onemes These are welcome trends in terminology but they are combined with a strong inclination to reject the influential role of environment in molding the patterns of treponematosis

He refers first to the differences between the syndromes of yaws and syphilis and asks what they could be due to Obviously he says they must be due to changes in one or more of the three host parasite and environment Now by selecting a series of negroes in Baltimore who have syphilis and a series of negroes

tern of treponematosis This view is supported by the fact that in transitional areas all stages in this evolution are present simultaneously

Treponematosis is a family disease If it is propagated freely among the children of the community, the resulting clinical entity is yaws If it habitually affects the adults first, the resulting clinical entity is syphilis In one the reservoir of the disease is the juvenile population, in the other the reservoir comprises the prostitutes and the males, married and unmarried, who patronize them This is pure epidemiology, and one can be sure that changes in the biological characters of both parasite and host are taking place pari passu with the change in epidemiology

In 1936 Saunders and associates[109] wrote on "The relationship of certain environmental factors to the distribution of yaws in Jamaica" The following statements are taken from this article 'Whereas yaws has been common in Jamaica for well over 200 years and has undoubtedly been introduced repeatedly into all parts of the island, it became localized in certain areas The present distribution corresponds almost exactly with that which existed 20 and 40 years ago" The general impression among yaws patients and doctors is that rainfall increases the disease Yaws cases are more numerous in the rainy season and in rainy places A smaller percentage of the population have lesions after a long dry spell, and there are more infectious relapses in the rainy season In no place where there is low annual rainfall is there a high incidence of the disease There is thus a distinct correlation between rainfall and yaws prevalence, and it seems there must be a minimum of about 50 inches of rain a year for yaws to be common

Saunders and his associates found that in Jamaica there was inverse relation between yaws prevalence and geological areas of pervious white limestone formation 'The conception of geological formation affecting the distribution of yaws by virtue of the property of holding moisture and providing ample vegetation furthers our idea that moisture may have some direct effect upon the disease' They found no correlation in Jamaica between altitude and yaws prevalence

As to sanitation these writers also found an inverse relation between sanitary status and yaws prevalence although this was not exact Yaws is never found in clean homes, but among lightly infected districts there is the same variation in sanitary levels as among heavily infected, showing that sanitation is not the sole nor the deciding factor Incidence in the 10 to 14 age group in a small town was 26 per cent and in the adjoining rural area 52 per cent The general sanitary level was only slightly higher in the towns, and these investigators favor recognition of the fact that town children were not subject to trauma from vegetation as were their country cousins

Lastly the influence of insects was discussed *H pallipes* seemed particularly associated with areas away from white limestone and toward good soil and moist

racial re ponses developed by centuries in Africa will result finally in a purely venereal pattern Although this result is a practical possibility in Baltimore in Central Africa it is not In other words the habitat of a race is a part of it so far as its diseases are concerned there is an inherent environmental component in the concept of race For the purposes of this discussion yaws is integrated with the African race at home the black in the United States is an ethnological hybrid and is therefore not properly comparable

Turner also neglects the parasite in his comparison of Jamaica and Baltimore negroes He overlooks the possibility that much of the difference may be due to strain differences in a single parasite *T pallidum* developed from interaction over a long time with two widely different environmental matrices

As to age of the patient Turner says adults with early yaws show the same eruptions as their children and children with acquired syphilis in civilized countries show chancres and the same course as their parents It seems therefore that the age of the patient may be discounted as one of the important variable factors contributing to the differences between yaws and syphilis This however is too fine reasoning In yaws the spirochete has been passed through a succession of untreated children over a long period of time In syphilis the spirochete has been passed through a succession of treated adults over a long period of time also This epidemiological feature has done something to the spirochete in each case Under what Boyd calls the natural history of juvenile treponematosis the treponeme undergoes a kind of domestication The yaws spirochete is taken into the bosom of the family and shares the hut or tent with the same freedom as the calf the hen the lou e and the flea As a result it reacts in a certain fashion with either child or adult The converse is true of the treponeme of syphilis In dismissing age of patient as unimportant Turner has overlooked a strong environmental component operating over a long time period

As to portal of entry Turner says it is difficult to understand how this difference could possibly influence the course of either disease once spread of the spirochete from portal of entry has taken place He cites the fact that 38 Baltimore negroes with extragenital chancres had a subsequent course typical of syphilis and not of yaws The difference in the usual portal of entry of the spirochetes of yaws and syphilis therefore does not account for the marked differences noted between the clinical manifestations of the two diseases This conclusion disregards the long term effect on parasite and host of habitual nonvenereal and extragenital infections on the one hand and venereal genital infections on the other Experimental biologists are aware of the significance of site of inoculation Stokes says it was animal experimentation which fir t showed the importance of this factor

Turner says of crowding lack of cleanliness and scant clothing that they doubt

in Jamaica, who have yaws he proposes to make a comparison, measuring each of the variable factors as to its influence upon the response of the host to infection

Referring to his own and Saunders work in Jamaica, he agrees that there are strong indications that environmental factors have a determining role in the distribution of yaws, but he omits reference to the influence of environment on the parasite dismisses the influence of environment on host as improbable and says of external modifying factors that the principal one is the possibility of a vector The epidemiology of syphilis is even more restricted in his view, as he admits no influencing factor outside the human host To him the epidemiological difference between yaws and syphilis boils down to the sexual habits of the host in the latter and the possibility of a vector in the former This is too narrow an interpretation of the role of epidemiology In addition to other factors, Turner omits any reference to the molding power of time

As to clinical differences this investigator selects five, three of which he considers characteristic of yaws, 1) frambesiform, 2) infectious plantar and 3) mucosal lesions and two of syphilis 1) iritis and 2) acute meningitis Now he is ready to compare his two groups of negroes

As to race he observes that the negroes in Baltimore have syphilis and those in Jamaica have yaws ' It is evident, therefore that the factor of race is not responsible for the differences noted between yaws and syphilis " In the narrow sense of ' blood this may be true, although some might call attention to the admixture of white blood in the American negro But Turner's two groups of negroes are not comparable on the more fundamental ground that one group of negroes is " at home ' and the other is ' in exile " Race here is more than ethnology When it is said of the black race that it has yaws, black race means negroes in their aboriginal environment This is what Gordon means by race, when he remarks that manifestations of disease in our race are not necessarily those in another race, differing from ourselves in heredity, historical experience, culture and environment and in physiological and psychological reaction[47] This is what Hutchinson meant 50 years ago, when he said yaws was syphilis modified by ' race and climate He was speaking of the primitive black in Africa, not the emancipated and civilized black of the North American continent The processes of sanitation and civilization in the negro population of this continent have not yet proceeded far enough to wipe out all vestiges of the yaws pattern The medical literature is full of reports pointing out differences between syphilis in white and black in the United States This is because the American negro as an ethnic group still is in the transitional phase of treponematosis However as time passes it becomes clear that syphilis in the black in the United States tends to approximate more and more closely syphilis in the white Elevation of negro economic and sanitary levels toward those of the white population and fading of

each instance the particular disease was acquired from a case of like nature Despite the fact that these patients were living under essentially the same climatic and geological conditions there is no indication that the character of the various clinical manifestations was materially altered

In the first place this is looking at only one moment in time and neglecting the fact that time is an epidemiological factor which Nature requires to mold the pattern of disease Secondly the conclusion drawn is as though all the cases had fallen neatly into one class or the other either typical yaws or typical syphilis but no less than 55 cases were discarded which did not fit and in which no decision was made whether they were due to yaws or syphilis These equivocal cases constitute no less than 38 per cent of the series What we should like to know is what kind of cases these came from They are the most important cases in the series the key in fact to the whole situation but no further reference is made to them 44 per cent of those with lesions were typically yaws 18 per cent were typically syphilis and 38 per cent might have been either Here is the same old shading off that was observed in Chambers clinical differential table in *Weller s pathological specimens and Turner s rabbits The most natural interpretation* of this large group of indeterminate clinical cases is that they represent transitional forms of the disease between the imported juvenile origin rural treponematosis and the standard urban venereal form They suggest also that this flow from country to city from juvenile to adult and from nonvenereal to venereal is continuously proceeding in Kingston Far from being the static yaws to yaws and syphilis to syphilis which is claimed the figures show a large component of transitional yaws to syphilis

It is true that all three phases of this evolution are occurring under exactly the same climatic conditions but an epidemiological factor stronger than climate has supervened the influence of the urban milieu Climatic factors influence strongly the propagation of rural yaws but they cede precedence in the town to factors of housing clothing and sanitation One can predict from Turner s figures that if one could dip treponemes like mosquitoes or band them like birds the treponemata causing his 63 cases of yaws would if they and their descendants could be traced be discovered a few years later in a group of indeterminate cases and only a little later in indurated primary lesions For the spirochete survives in those portions of the body s envelope in which circumstances of human life permit it and the picture which treponematosis presents at any given time or place depends directly upon the habits of man

Neglecting his 38 per cent Turner thinks his figures suggest that once established each disease runs its course largely unmodified by factors which lie without the host but if the 38 per cent is included as it must be the reverse conclusion is inevitable Enthusiasm for the significance of the differences he

less enhance the opportunity for spread of yaws, but "there is not the slightest evidence which indicates that once an individual is infected the clinical course of yaws varies materially according to the conditions of hygiene and sanitation under which he lived" That is, he believes that a man, who has syphilis will have symptoms running true to syphilis no matter how crowded, filthy and naked he is and another man s yaws will remain yaws no matter how clean and clothed he is There are some who would challenge this sweeping statement but although it be accepted as fact so far as an individual is concerned, it is not the same as saying that a treponematosis, which runs through a series of generations of crowded, filthy and naked human beings, will turn out the same syndrome as one which has run through a series of generations of well sanitated and clothed people As an illustration of the influence of social and economic factors one has only to review the evolution of treponematosis in the negro population of North America in the last 300 years

To estimate the influence of climatic factors Turner went to Kingston, Jamaica a city of 90 000 "For years it has been known that new cases of yaws arise very seldom within the city, but that because of the ease of communication with other parts of the island infectious cases of yaws are being constantly introduced into the city" Heavily infected yaws districts lie within 10 miles of the city He felt that, if syphilis and yaws as found in Kingston were "typical" under the same climate, then climate as an epidemiological factor would be canceled out This assumed that all other variables were controlled, which was not the case but the project nevertheless promised to be interesting A special clinic was set up in the city to which those patients were admitted, whose blood tests were positive, and/or who showed on cursory examination some lesion suggestive of yaws or syphilis

The series comprised 380 patients of whom 144 had treponematous lesions 201 had no abnormality except a positive Wassermann reaction and 35 were free of treponematous infection Of the 144 with lesions, 63 (44 per cent) had lesions characteristic of rural yaws cases 30 frambesiform 10 infectious plantar and 23 plantar hyperkeratosis None of them had iritis or mucosal lesions, 44 were under and 19 over, the age of 15 Twenty six (18 per cent) of the 144 patients had lesions characteristic of syphilis, 5 indurated genitals primaries and 21 typical secondary syphilides (in 11 signs of the chancre were still present), 6 had iritis and 9 mucosal lesions 15 of the 26 syphilitic patients were old residents of Kingston with continuous residence of 5 years or more, 4 had lived there for something over a year and the remainder for shorter periods On the other hand, although the 63 patients with yaws lesions were all residents of Kingston, 59 of them had acquired their infections in neighboring yaws communities and their first sores were in extragenital sites Turner comments "There is every indication that in

but it is necessary to face another fact about treponematosis which creates a dilemma for the static viewpoint for this versatile disease occasionally reverses itself and changes back from adult venereal to juvenile nonvenereal The dynamic interpretation accepts such an event with equanimity in fact it accepts this phenomenon as proof of its own soundness But the static view which draws the picture as if there were two diseases which have been diverging on their respective highways since remote antiquity is hard up to explain how syphilis for example can lose its venereal aspect and come to look like yaws The conventional interpretation being too rigid to anticipate such an eventuality finds distasteful the concept of such a metamorphosis taking place within historical times and even today

The evolutionary interpretation welcomes transitional forms like bejel intermediate forms like the syphilis of the Russian peasant and the southern negro and variations of treponematosis like pinta and gangosa including them all as clinical entities of a great human disease The static interpretation is forced to give separate disease status to each of the various forms such as yaws bejel and pinta or group them under the generic term syphiloid This wholly unscientific name is just as much an artefact as the medieval word leprosy and like it must remain in quotes There have been many syphiloids in medical history all of them caused by *T pallidum* Many of them had their origin in venereal syphilis but changed to a nonvenereal juvenile character in response to changed conditions of human life Since these syndromes did not conform to the superficial and epidemiological features of venereal syphilis they were called by individual names or dismissed as like syphilis This section will describe the principal examples The syphiloids are either the present day representatives of the primordial treponematosis or they represent atavisms and reversions to that primitive form They demonstrate historically that the tide of treponematosis can ebb from venereal to nonvenereal as well as flow from juvenile to adult patterns

Sibbens Button scurvy and Radesyge

Shortly after Cromwell s campaign in Scotland there appeared in the neighborhood of Inverness and the Highland counties a very contagious disease characterized by an eruption on the skin and mucous membranes and leading to ulcers pain in the bones and erosion of the nose It ran through families affecting children and women as well as men Chancres were not seen infections were recognized as being extragenital and acquired through the medium of common utensils the hospitable passing of the common pipe and the habit of crowding children and adults together in sleep First reports arose in 1640 and the disease was still lingering in some remote places in 1771 when Ebenezer Gilchrist of Edinburgh

found in rabbits testicles has lead Turner to throw overboard most of the accumulated evidence that in treponematosis the environment is modifying the host and the parasite and consequently, the clinical pattern of the disease Indeed the very quantitative differences, which he found in his rabbits are logically attributable to physiological variations in the treponemes produced in them by pressure of environmental forces Although admitting that "it is not difficult to conceive of the *Treponema* group of organisms undergoing substantial biological changes in response to variations in hereditary and environmental factors , he rejects the possibility that the differentiation between yaws and syphilis first occurred within historic times He sees them as static entities The succeeding section will show however that yaws and syphilis have surprising fluidity, and that the evolutionary factors, far from belonging to the prehistoric past, are features of the living present

THE SYPHILOIDS "

In the foregoing sections treponematosis has been interpreted as an ancient and world wide disease caused by strains of *T pallidum* and attacking man in one of two ways So far as the treponeme is concerned, it is a happy circumstance that the uncivilized people of the world live in humid tropical regions, for the combination of primitive man s indifference toward disease and the presence of moisture on his skin ensure the perpetuation of nonvenereal juvenile treponematosis It is also a happy circumstance for the treponeme that, as the process of civilization proceeds in temperate climates and the opportunities for transmission through the juvenile pattern fade, adult sexual intercourse both promiscuous and legitimate, takes over the role of transfering the parasite from one moist surface to another According to this view the fundamental pathological processes of treponematosis within man s body are the same everywhere, but the external appearance symptoms and signs of the disease assume one or other clinical pattern depending upon the environmental framework

The conventional interpretation on the other hand begins with the two clinical patterns and assumes that they represent two different parasitic diseases one limited by definition to the tropics and one more generally distributed The first interpretation is dynamic based upon the principle of functional variation the second is static based upon the concept of two fixed diseases and the displacement of one by the other According to the first view there is a continuous and common foundation beneath both forms of disease the conventional view, on the contrary, finds them already so far apart that they have only an ancestor in common

As long as discussion concerns solely the flow from child to adult, from nonvenereal to venereal and from primitive to civilized man, either view is tenable,

Here again a venereal treponematosis reverted to a nonvenereal type under the influence of epidemiological factors As in Scotland and Ireland this syph iloid persisted as long as the conditions which gave it birth With improvement in the living conditions of the peasants the disease faded and it persists today only in medical history a witness to the adaptation of the treponeme to the human environment

Skerljevo and Others *

This is a Croatian word, and along the coast of Dalmatia in Bosnia and Herzegovina as early as the end of the 18th Century it stood for a common disease of the country people very contagious and characterized by eruptions ulcers and necroses affecting both young and old It was said to have come originally from *sailors soldiers and prostitutes but it had lost all venereal significance in the early* 19th Century Synonyms were numerous such as mal di Fiume mal di Ragusa mal di Breno frenjak (the foreign) and the fumigating disease Investi gation by officials showed many leprosy like ulcers and eczemata and special hos pitals were established for skerljevo Disinfection isolation control of marriage and other means were used to arrest the infection and these were partially suc cessful They were discontinued later however and since the fundamental habits of the peasants were unchanged the disea e returned It was recognized as of syphilitic nature but still was confused with leprosy and scurvy In a second campaign which lasted *10 years 41 000 patients were treated but again the dis* ease returned In 1880 after the Congress of Berlin gave Austria Hungary the right to occupy Bosnia and Herzegovina skerljevo was attacked again It was observed that whole villages were infected and there were epidemics among the school children so a campaign of prevention and education was combined with iso lation and treatment Gluck who had charge of this campaign reported several foci wiped out in 1903 but even today the disease stubbornly appears at remote spots where conditions are right for nonvenereal propagation

Many have called attention to the similarity between skerljevo and the vene real leprosy of the Middle Ages *The rarity of chancres the prevalence of ex* tragenital and innocent infections the universal distribution of the disease in the rural communities and villages all are common features Gluck listed the follow ing symptoms 1) pain in the bones especially at night 2) rarity of the roseola and frequency of the circinate papular syphilide 3) frequency of moist condylo mata pustules ecthymatous and rupial lesions 4) preponderance of mucosal lesions in early cases (55 per cent) 5) frequent mucocutaneous relapse especially in the children with hypertrophic papules of genitals scrotum and anus 6) hyper pigmentation followed by depigmentation 7) parchment scars cicatrices and deep

described it[14] It was believed to have originated through venereal contacts between Cromwell's soldiers and the rural people, but it had lost its venereal quality subsequently Some called it frambesia cromwelliana and others epidemic or endemic syphilis The people themselves called it sibbens (or sivvens), which Hutchinson says is the old Erse word for raspberry [1] Macqueen[53] says that Manson considered it possible that sibbens was really yaws

About the same time there appeared in Ireland among the peasants in remote districts a similar contagious disease which they called berry eczema or button scurvy This followed the same nonvenereal course, propagated under the miserable conditions of peasant life of which Scott[11] has given the following composite picture "The conditions under which the poorer persons lived were conducive to intimacy and spread of any infection The dwellings were mostly sod huts of green turf, erected merely on the ground, with no real foundation, few of the rooms were boarded, the turf absorbed moisture and became like a soaked sponge Windows were few, the openings were nailed up in winter, stopping all ventilation In some the peasant and his wife would have a separate bedroom, but among the poorer all the people on the farm men, women, and children might sleep in one room, and they also took their meals there The beds were merely wooden boxes large enough to accommodate(!) two or three sleeping head to feet The air consequently was foul and unwholesome, cats dogs and children would play and lie on the dirty reeking floor "

These conditions were duplicated in the Scandinavian countries About 1700 there appeared in Norway a contagious disease said to have arisen from venereal contacts of Russian sailors with the peasants This was of the same contagious character and the name, radesyge, appeared in 1743 The clergy considered it 'familial syphilis ', but some physicians thought it leprosy complicated with scurvy or a 'degenerated form of syphilis complicated with scrofula, ringworm or scabies Hjort in 1832 studied radesyge in south and west Norway and decided it was a disease sui generis Finally Boeck in 1860 ascertained that it was syphilis and differentiated it from leprosy Sweden's first clear record of radesyge was in 1762 but it was present long before that date It was said to have been brought by travellers or sailors and soldiers coming home from the incessant wars of the time It was spread particularly at times of herring saltings and other festivals Chancres were rare, and extragenital infections the rule propagation including men, women and children indiscriminately There were profuse eruptions of skin and mucosae with eroding ulcers of palate nose and larynx Some physicians identified it with 'sibbens" others thought it a composite of syphilis, scurvy and leprosy The doctors felt it beneath their dignity to treat such a foul peasant disease and although special hospitals were established in some places, the treatment fell largely into the hands of quacks[18]

dence of the disease was 100 per cent in the rural villages but became rarer in the towns, in fact, the larger the population the less of this type of syphilis was found

Von Duhring believed that this nonvenereal syphilis was introduced into Turkey in 1829 by Russian troops in the War for Greek Independence If this was true it affords another illustration of metamorphosis from venereal to non venereal pattern The reason why this nonvenereal type was confined to the rural villages was that as in Kingston Jamaica the urban milieu broke down the usual nonvenereal avenues of propagation and substituted opportunities for venereal spread Von Duhring repeats the error of considering the profuse pathology a sign of virgin soil neglecting the fact that such pathology is found wherever the treponeme is given a free rein especially in those areas where the soil is least virgin as in Central Africa or Haiti

Macqueen in 1931[68] published a description of what he called syphilis insontium in Palestine He remarked the close parallel to skerljevo in the Balkans von Duhring s endemic syphilis in Turkey and even sibbens in Scotland The principal focus of the Palestinian disease was Hebron and it was said to have been brought in by Ibrahim Pasha s troops in the 1840 s and by sub equent conscription of men for the Turkish army If this origin is correct a further illustration is provided for the metamorphosis of treponematosis from adult venereal to juvenile nonvenereal type for Macqueen found the disease preponderantly among the children and slightly more among females than males Extragenital infection accounted for three fourths of the cases comprising play contacts among children of pre school and school age the use of common utensils and drinking vessels the friendly haring of coffee cup pipe and narghileh and the caressing of children by adults (the Arab is a lavish ki ser) As John Brickell said of yaws in North Carolina Macqueen also noted that no shame was attached to the disease and that it was not associated with gonorrhea

Chancres were found in less than 1 per cent of the cases a mucocutaneous eruption was characteristic with a preponderance in favor of the mucosae of the nose and throat Every second or third patient presented mucous patches which were producing discomfort and interfering with eating No true ro eola rash was found in several hundred cases condylomata and papular annular and circinate lesions were frequent not uncommonly with rupial tendencies Among late lesions gummata of skin and subcutaneous tissues predominated with osteoperiostitis and nasal and palatal erosion Abortion was not more frequent than in healthy women the disease was not commonly transmitted congenitally and he never saw snuffles rashes in the first three months Hutchinson s teeth or interstitial keratitis Only one tabes and one paresis case were observed in a series of over 2 000 patients

Macqueen also noted the relation of this disease to the small villages of the

confluent ulcers 8) loss of nose, lips, eyelids and even eyes, necrosis of pharynx and larynx These are the " terrible tertiaries " so characteristic of treponematosis when it is left to itself Especially to be noted is the absence of tabes, paresis and evidence of visceral involvement

Endemic syphilis of this nature was described in Greece (called spyrocolon), Lithuania Esthonia, Courland, Hesse, Serbia the Crimea and many other parts of Russia in the 19th Century There were transient outbreaks of nonvenereal treponematosis in France (mal de St Euphemie, 1797), (mal de Chavanne Lure, 1818), (pian de Nevac, 1875) in all of which men, women and children were involved In 1760 there was an outbreak on Murray Bay in Canada, said to have been brought by sailors from Normandy and expressly described as resembling morbus gallicus Juvenile infection characterized all these " syphiloids " In Russia one reporter said the greatest incidence was in children of 2 years, another reported seeing gummata in children of 5 in the Ukraine 30 per cent of the cases were between 6 and 15 years old Two thirds of the cases were in women and children and it was remarked that the men brought the disease home and the women and children cultivated it[48]

It was generally accepted that infection usually was via the mouth Children thus contracted it from each other at play, wetnurses were a menace, unclean utensils were blamed as well as common pipes and cigarettes, the Holy Communion and other drinking vessels the hospitable lodging of strangers in the peasant huts, the crowded sleeping quarters, the presence of lice, fleas, flies and cockroaches Immorality played but a small role there was some promiscuity but little prostitution in these rural communities Circumcision, tattooing, vaccination, licking foreign bodies from the eye with the tongue prechewing of infant food and other practices were blamed at various times There was ignorance of cause and indifference of infected people or parents, lack of isolation and treatment The doctor often saw only the late (tertiary) cases, since the early eruptions generally were thought to be self terminating[48] One point is to be emphasized this endemic treponematosis very rarely caused death Here is potent support for the view that the reported mortality associated with medieval syphilis was due to other causes

Von Duhring[1] described endemic syphilis as he found it in Turkey during the closing years of the last century Chancres were very rare and secondary manifestations almost confined to children In other words the child population was the reservoir of the disease Late lesions consisting of skin ulcers and gummata swellings of bones and joints and erosion of palate and nasal bones occurred in adults and reminded von Duhring of descriptions of syphilis in the 16th Century Among 80 000 cases he saw none of tabes or paresis Infant mortality was high but congenital cases rare Most infection was by extragenital routes Inci

particularly of the long bones with formation of sabre shins adenopathy, juxta articular nodules hyperpigmentation depigmentation hyperkeratosis and alopecia An adult who has escaped bejel in childhood, is likely to contract it later from a child, often his own The course of the disease in the adult does not differ essentially from that of the child *Hypertension* is virtually unknown in the Arab, and he does not suffer from aneurysm meningovascular syphilis tabes and paresis are exceedingly rare Bedouin women who have had bejel do not ordinarily transmit it to the fetus abortions and miscarriages are not more frequent among them than among neighboring groups of women

That bejel is treponematosis is established by the character of its early and late lesions the quality of latency the uniform presence of a treponeme indistinguishable from *T pallidum* the positive precipitation and complement fixation reactions and the favorable response to antitreponemal drugs It is a juvenile disease acquired nonvenereally existing almost wholly without regard to sex It is found in both sexes and all ages and to the same degree in the sick and presumably well components of the Bedouin population among them it is well nigh universal[89]

It is noteworthy that as in yaws and the other nonvenereal 'syphiloids chancres are seldom if ever observed in bejel and there is no shame attached to the disease There is no associated gonorrhea On the other hand both chancres and gonorrhea are common among the townspeople of the same region A clear distinction is made by the clinic patients between bejel the juvenile disease of the bedouins and franghi the venereal disease of the town The semi nomad bedouin does not mind having bejel but he resents any suggestion that he might have franghi for he distinguishes their respective epidemiologies Thus within a very narrow geographical compass are to be found the two clinical patterns of treponematosis an exact parallel to the situation in Kingston and its surrounding rural area

Bejel is indistinguishable from yaws in nonvenereal juvenile acquisition community wide dissemination absence of chancres and congenital transmission morphology of the skin lesions relative escape of the eyes the cardiovascular system the central nervous system and the viscera the lack of constitutional disturbance the lack of infantile dystrophies the failure to impair fertility and virility and the presence of gangosa juxta articular nodules and patchy depigmentations Both bejel and yaws tend to disappear rapidly when brought into contact with civilizing influences In both the problems and the methods of treatment are the same On the other hand bejel is indistinguishable from syphilis in its constant involvement of the mucous membranes in the early stages in the occasional finding of alopecia in many of its general pathological aspects and in its extra tropical geographical location One can either discount all resemblances

rural areas and the fact that it faded out in urban environments In the small village of Nahalin (pop 380) 23 5 per cent had obvious lesions and over a third of these patients were under 10 years of age A grandmother (aged 60), her four children (aged 16 20, 22, 25) and four grandchildren (aged 1, 2, 3 3) all had secondary lesions at the same time Such distribution of age confirms the non venereal epidemiology

Bejel

Bejel was presented in 1928[64] as a spirochetal disease due to *T pallidum*, a variant of the syphilis yaws ' treponematosis, found among the Arabs of the Syrian desert Subsequent articles established the juvenile character of bejel, its high incidence in the bedouin communities its uniformly positive serological reactions its ready response to anti syphilitic treatment and its numerous points of identity with yaws Darkfield studies showed that it was due to a treponeme identical with *T pallidum* In 1937 the information about bejel was summarized[66], and it was stated that the Arab word, bejel, had been introduced into the litera ture solely to distinguish this nonvenereal syphilis from the venereal implications associated with the word syphilis as ordinarily understood

Whence bejel came is unknown The Arab word which thus is transliterated is probably an old form meaning ' sores " There is nothing in the nature of the disease or in the attitude of the Euphrates Arabs toward it to suggest that bejel is a recent importation in fact presumption points the other way The Arabs have been traders in African slaves since time immemorial It was along the Euphrates that the " curse " first appeared, and isolation was first practiced Mer cury was traced to Syria by Fracastoro and brought from there to Europe by the returning Crusaders

The clinical course of bejel is briefly as follows At some time in early life the Bedouin child contracts bejel from some other child in the acute stage of the disease The spirochete usually is passed from host to host by immediate, non sexual contact and the transfer is favored by general uncleanliness, total lack of segregation and the succulence of the mucocutaneous lesions Possible auxiliary factors in contagion are the use of a common drinking bowl, the habit of kissing and fondling children and the presence of the domestic fly the louse and the flea Lesions often appear first in the mouth but are soon followed by moist papules in the folds of the skin and by drier lesions on trunk and extremities Treponemes are easily demonstrable in great numbers in all these lesions A roseolar eruption has been observed but is rare Late lesions consist of ulceration and erosion of palatal and nasal bones which involve pharynx and often larynx gummata of skin and subcutaneous tissues producing huge ulcers and cicatrices osteoperiostitis

Pinta

This is one of the most interesting forms of treponematosis and a good example of the confusion into which the conventional interpretation leads Depigmentations have always been a feature of late treponematosis Light spots on dark skinned races tend to blue pink and white shades Loss of pigment was one of the features which continually led to confusion between treponematous infections and leprosy As Holcomb says there was an infectious or contagious element in many such lesions described in ancient Hindu Greek Arabic Latin and Romance medical texts Alzaharavius (about 950) called this discoloration al baras which was hereditary and venereal Constantine in the 11th Century called it morphoea and John de Vigo (about 1500) classified it as a feature of morbus gallicus Holcomb cites descriptions of this treponematous depigmentation in India the Straits Settlements Egypt and Tunisia where formerly it was called lepre Kabyle Classic examples of pinta have been photographed in bejel and by Lacapere in Arab syphilis in Morocco Gluck mentions depigmentation in skerljevo and there are numerous references to it in yaws both in the New and the Old World Holcomb has collected from various countries a number of names including lepra blanca and leucoderma syphilitica Others are tina empeines carate and vitiligo Mal del pinto is a variation of pinta and is translated erroneously Pinto s disease in an editorial[3] as though Pinto were a personal name

Pinta was described as a separate disease in Mexico as early as 1757 and Holcomb says the name originated there A commission which reported on the disease as early as 1811 called it leprosy In 1889 Tellez for the first time recorded the idea that pinta is an exanthematic form of syphilis and is transmitted by venereal contact Berecochea and Corona in 1811 spoke for the first time of the beneficial effects of mercury and later in the century the Indians who had it found that working in the mercury mines made them feel better On this basis Gratz proved the effectiveness of arsenic in 1913 The uniformly positive Wassermann reaction was demonstrated in 19 5[4]

In spite of all this evidence of the treponematous nature of the disease it continued to be treated in the textbooks as a specific depigmentation due to a fungus It was not until the discovery of a treponeme by a Cuban group in 1938 that its spirochetal origin was acknowledged This parasite although never differentiated in any way from either *T pallidum* or *T pertenue* was assumed to have a right to a separate name Unfortunately it was given no less than six but *T carateum* has the priority

Pinta is an extremely chronic clinical entity usually beginning in childhood and lasting practically for life Rare instances of venereal infection and congenital transmission have been reported[5] It is rare in whites being found prin

to syphilis and say that bejel is yaws modified by a desert climate, or one may identify it with syphilis as seen under the epidemiological conditions of a semi nomad and desert people In fine, there is no clear cut differential between bejel and yaws or between bejel and syphilis It is a variant of treponematosis, one of those transitional forms, which prove the essential one ness of this versatile disease of man

This view is a stumbling block to those who believe that syphilis and yaws are essentially different diseases, caused by different parasites There have been various attempts to 'explain away' bejel Some have claimed on ipse dixit grounds that bejel is just ordinary syphilis and its nonvenereal feature a myth others insist on regarding it as a third disease different from both syphilis and yaws These dislike the suggestion that the cause of bejel is *T pallidum* and suggest that it is caused by still a third treponeme It would suit them better if the parasite of bejel had been given another specific name Thus one comment runs, ' I notice you state that this condition is caused by *T pallidum* and I am wondering how you can prove that this is so beyond the fact that it has the same morphology as *pallidum* It seems to me it is a matter of opinion whether the spirochetes causing yaws syphilis and bejel are one and the same, or whether they are good species The fact that they are indistinguishable in morphology does not prove that they are not good species " (personal communication) The reply of course is that the proof that bejel is caused by *T pallidum* is exactly the same as the proof that syphilis is caused by *T pallidum* viz , identification of the parasite in the darkfield constancy of serological reaction, constant presence of certain definite fundamental pathological processes and response to specific treatment Suppose the question were turned around, how could one prove that bejel is not caused by *T pallidum?*

If as seems reasonable syphilis and bejel are both caused by the same parasite a logical corollary would be to regard *T pallidum* as the cause of yaws also for bejel demonstrates that the environment produces many of the well known differences between syphilis and yaws and a rapidly diminishing residue of differential points remains Life is not a still but a moving picture and the study of diseases in relation to their environment throws light on their relationships The tool of epidemiology is time and the environment working with time can mold parasite host and disease syndrome The significance of bejel is that it places fresh emphasis upon the influence of environmental factors in the production of the various clinical entities which make up treponematosis Bejel to those who have described it has never been a disease sui generis When it has served its harmonizing role among the various clinical entities of treponematosis the word bejel should pass into medical history along with the words sibbens and radesyge[68]

The pigmentary changes first appear in the tertiary or late stage As Fox[6] says most of these cases are observed in adults and until recently they were thought to be the sole manifestation of the disease He says there are two striking colors white and blue the former indistinguishable from ordinary vitiligo The bluish patches are more characteristic located on uncovered parts of the body, face neck and especially the extremities with predilection for the bony prominences the hands and the feet the front of the wrist and the scrotum There is symmetry and the disfigurement in the vitiligoid stage is permanent

The histopathology of these depigmented areas reveals keratoderma and superficial atrophoderma Pigmentary function is disturbed there is scaling in one third itching in one fourth and mucous membrane patches in one fourth[6] Pardo Castello says there is a lack of pigment granules in the basal epithelial layer and the presence of enormous numbers of melanophores in the upper part of the corium Atrophy of the epidermis is an almost constant feature The cellular infiltrate shows predilection for the vicinity of the blood vessels and toward the edge of the lesion the infiltration occurs exclusively in perivascular patches The endothelium of the blood vessels is swollen and the vessel walls are invaded and at times dissociated by the infiltrating inflammatory cells In the final white patches there is absent pigment atrophied epidermis disappearance of papillae and sclerosis of connective tissues These obviously represent the final atrophic cicatricial stage at the end of the inflammatory process Specific treatment as would be expected has no influence upon these lesions nor are they in any way contagious They have been found however to be associated with such characteristic spirochetal pathology as plantar and palmar keratosis changes in the gold curve of the spinal fluid juxta articular nodules and adenopathy in two thirds of a small series in Cuba there was an aortitis[9]

One cannot say that pinta is distinguishable from other forms of treponematosis by reason of its pathology for from beginning to end its histopathology is fundamentally that of treponematosis There is only a quantitative difference in the degree of vascular occlusion tissue sclerosis and consequent dermal atrophy This does not justify making a disease out of all cases of syphilis and yaws which happen to concentrate their late manifestations in the direction of pigment disturbance and skin atrophy By the same token one might assign a different name and parasite for example to those cases of malaria which display cerebral thrombosis

It must be plain to all who are not influenced by preconceived ideas that in pinta a physical sign or symptom of late treponematosis has been elevated to the position of a disease sui generis This view does not detract from the value of the experimental work of Blanco and others [9] but does question the correctness of

cipally among the lower classes such as negroes, native Indians and mestizos A rural disease, it appears among laborers, agricultural workers and people living under unsanitary conditions Fox[41] suggests that the hygiene of white people accounts for their comparative freedom from this infection, an example of epidemiology at work It tends to greatest incidence in certain river valleys, and "pintogenous zones" have been described Vectors have been suggested but none accepted Infection seems to be by skin contact

There is no primary lesion in the sense of a chancre The disease begins as an extragenital papule which becomes, as in yaws, part of the disseminated secondary manifestations and cannot be distinguished from them [3] The usual site is on a lower extremity suggesting that, as in yaws, trauma may play some part in its location The original papule in the course of 7 to 20 days becomes an erythemato squamous patch or plaque with a circinate configuration Within 5 months this original pintid, as it is called, has been succeeded by a general eruption of the same nature resembling "psoriasis, ringworm, syphilis, eczema or leprosy", but retaining the circinate tendency[41] Sometimes the eruption which usually is on extremities and face involves the palms, soles, mucous membranes and male and female genitals[6]

The histopathology of early cases is distinctively treponematous, consisting of hyperkeratosis, acanthosis, intercellular edema increase of lymphocytes and plasma cells and perivascular and endothelial infitration[40] The serology becomes positive early and increases slowly in degree of reaction, both in precipitation and complement fixation tests The positivity is said to be particularly "fast" in spite of treatment[5]

Up to this point this is a perfect story of a "syphiloid" or a juvenile form of treponematosis Pardo Castello[98] says the similarity to yaws makes differentiation difficult In fact the dry, patchy, non ulcerative lesions, which the Haitians call bubas secas (dry yaws) and the natives of Cuba call by the old medieval word empeines always is associated with treponematosis Pardo Castello says the medical profession in Cuba always disregarded their patients frequent claim that their mal del pinto started with empeines That is, for decades doctors refused to link pinta with what were obviously spirochetal lesions and persisted instead in attributing the color changes to the action of some fungus or other Yet de Isla connected empeines with bubas, spreading on the edge and healing in the center and Corona (1811) in Mexico called the disease tina (tinea) and said it appeared in the form of empeines, spreading from the center and developing black, blue or white spots later Tina was also used in the Middle Ages as a synonym of empeines[4]

The attention of the profession was focussed on the late dyschromic lesions, and they failed to connect them up with the antecedent spirochetal infection

who have described yaws at different times and places and the notoriously patchy and spotty distribution of that disease

Mention has been made of the presence of aortitis adenopathy juxta articular nodules and other late signs of spirochetosis in pinta Fox[40] says no bone lesions or gangosa have been associated with pinta If this is accepted one must assume that, when depigmentation is associated with bone lesions and gangosa it is due to yaws and not to pinta which is begging the question In the same way when Fox[9] says pinta does not cause subjective symptoms and does not affect the general health when he says it is not a serious disease except for the cosmetic defect one remembers that many if not most late cases of treponematosis of the rural, childhood acquired type end up apparently well and one must realize that the specifications of this artificial disease are so drawn as to exclude many cases which would not fit this pattern When he says[4] the clinical appearance of the pigmentary or dyschromic stage is often characteristic and does not simulate any other known disease one remarks the word often and remembers that he also says[40] that the white depigmentation in pinta is indistinguishable from vitiligo As to being unlike any other disease there are many signs in clinical medicine which are unlike other diseases but they are not by virtue of that fact set up as independent diseases As will be seen gangosa was erroneously given such a status but it has been drawn back into line In malaria the thrombosis of cerebral capillaries due to stickiness of the red cells is also unlike any other disease but no one proposes a different name and a different parasite for this phenomenon on the ground that not all malaria cases show it and that it is unlike any other disease

Irkintja

This is the name given by the Australian aborigines to their juvenile treponematosis Cleland reports that Sturt who made an expedition to the Murray River in 1830 found a loathsome disease among the primitive people of that region characterized by violent skin eruptions glandular affections loss of nose and even of sight Not even the youngest infants were exempt Sturt who was not a doctor called it syphilis and leprosy It is known that the Portuguese first touched Australia in 1511 and 1529 and one theory of the origin of irkintja is venereal infection of the natives by the early traders and whalers Hackett finds good ground for believing that the disease was widespread in Australia long before the coming of Europeans and it would therefore be a part of the treponematosis which was disseminated by the Proto negroid migrations Hackett translates irkintja as yaws as does Basedow[3] who spells it errikincha. The latter says the native name for syphilis is kirkni or kududu Like other primi

their interpretations Following the precedent of yaws, these investigators gave the treponeme of pinta a specific name, in spite of the fact that so far as anyone could tell it was *T pallidum* Then all the late cases of treponematosis in Central and South America, which showed depigmentation, were delivered over to the "new" disease caused by the "new" treponeme

Overlooked was the fact that pinta starts out exactly as many other cases of juvenile treponematosis, is indistinguishable from yaws, for example, for years and can only be diagnosed a posteriori upon the appearance of the late dyschromic stage Neglected was the fact that depigmentation is one of the hallmarks of late treponematosis everywhere The strong suspicion arises that pinta is caused by a parasite of an artificial species and comprises those cases of treponematosis which show the particular symptom of pigment disturbance If one should take the description of pinta seriously one should call by this name all the depigmentation cases in all the forms of treponematosis in the world Until recently pinta has been limited to Central and South America but the process of expansion is beginning As the editorial[32] previously referred to says, " it would seem that the disease is prevalent in practically the whole American hemisphere" Lieberthal[33] reports that he has found three cases in Chicago, and a report comes from Argentine There is no reason to limit the trend to the New World Observers in Guam (personal communication) are finding it there Soon, wherever treponematosis is found, pinta will be reported Once a physical sign is dignified with the status of a disease its distribution will grow until it coincides with that of the disease of which it is a sign, pinta may turn up anywhere there is treponematosis, especially of the juvenile and untreated type

It is estimated that there are a half million cases of pinta in Columbia, 55 000 in Venezuela 300 000 in Mexico and similar numbers in other Central and South American countries[6] These are larger figures of treponematous depigmentation than have been reported in other areas of the world, but nowhere else, in Africa, for example, have we figures of the incidence of depigmentation, which can be used for comparison for in other countries such depigmentations are still considered a sign of yaws Certainly there is a very close relation between the epidemiology of pinta and yaws and one requires to know the relative incidence of these two syndromes in the American areas in which pinta is so prevalent It may be that in these areas yaws cases have an unusual tendency toward depigmentation in their late stages This might be attributed to a strain of *T pallidum*, which particularly affects the pigmentary functions of the skin, except for the fact that this depigmentation occurs in all countries and one would have to assume the independent appearance of such a strain in many places Certainly various types of treponematosis tend to show preponderance of one sign or another in various parts of the world This accounts for the great diversity among those,

who have described yaws at different times and places and the notoriously patchy and spotty distribution of that disease

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tive people they distinguish between their childhood treponematosis and the imported venereal disease of adults The climate is extremely dry in large areas of central Australia and consequently the early eruption is more conspicuous in the mouth than on the skin Later, there are tertiary skin lesions, ulcers, adenopathy and gangosa

Irkintja provides another illustration of the predominance of a particular type of treponematous pathology in a certain area Here it is bowing of the tibiae the so called boomerang leg [1] Overgrowth of the tibial crest following inflammation of the periosteum causing sabre shins is found in all patterns of treponematosis but particularly in yaws bejel and other rural forms It has been thought that trauma is responsible for this localization on the vulnerable skin In irkintja after the early stage in infancy and childhood there is a quiescent period of some years and then pains in the shins develop, and the tibiae become bowed forward with the production of boomerang leg practically always before puberty Why these aborigines should have sabre shins in this exaggerated form found nowhere else in the world, is not clear Apparently there is something in the environment of the disease, something in the habits or diet of these people, which produces this bizarre effect through interaction with the spirochetal disease processes It is noteworthy that irkintja and boomerang legs persist in Australian aborigines as long as they are not divorced from their bush fashion of life, but that both tend to disappear and fade into transitional treponematosis as economic and hygienic standards begin to rise Basedow[3] says this "native syphilis", when it appears is remarkable for three things a) less conspicuous primary and secondary manifestations b) profuse tertiaries (gummata) of the skin and bones and c) absence of tabes and paresis, all characteristics of the transitional form elsewhere

Yaws

This clinical entity has been discussed in the preceding sections from the standpoint of etiology symptomatology epidemiology pathology and diagnosis It is discussed also in Chapt XXIX of this volume As to treatment two tendencies are apparent One is represented by Fox[39] who says yaws may be permanently cured in the early stages with three injections of neoarsphenamine, and the other by Pardo Castello and Chambers, who have studied yaws in Cuba and Jamaica respectively Pardo Castello[98] says yaws is as difficult to cure as syphilis "One feels inclined to say that yaws is incurable in a large proportion of cases and that the treatment should be as for syphilis early vigorous and continuous The latter (1944) takes issue with Fox stating that it is inaccurate to say yaws is cured' Relapses occur even after serological reversal, and in the majority of cases the

Wassermann reaction remains positive even after 6 injections He says it is out of the pool of latent blood positive cases that most relapses arise Experience with bejel supports the view of Pardo Castello and Chambers

Although Fox in discussing Pardo Castello s paper agrees with him that yaws is a serious condition and one that is difficult to cure he later[41] repeats the statement that yaws is much milder than syphilis its prognosis immeasurably better and that 3 injections often result in complete cure Such statements are unfortunate and misleading Infections are being occasionally acquired by servicemen in the tropics it would be regrettable if the conduct of such cases or of campaigns against yaws in natives should be undertaken in the spirit of this pronouncement It is true that these strains of *Treponema pallidum* have not been subjected to previous exposure to treatment and the immediate effects are often dramatically satisfactory but the only safe attitude is to remember the extraordinary adaptability of the treponeme and if cure of the individual is the goal to pursue the treatment of yaws with the same methods and the same assiduity that is regarded as good practice in the treatment of syphilis In other words there is no qualitative difference between these two patterns of treponematosis either in respect to treatment or to prognosis

Before leaving yaws it is necessary to glance at three of its sequelae which have received considerable attention One of them *gangosa* was for a while set up as an independent disease and another the *nodules* was erroneously thought to be found only in yaws The exact nature of the third called *goundou* is still sub judice

Juxta articular nodules have been described in the past 40 or 50 years as hard insensitive tumors of slow evolution ordinarily symmetrical and with little or no tendency to disappear situated near elbows knees trochanters ischial tuberosities and other bony prominences remaining for years unchanged although responding favorably and rapidly to specific therapy The ites suggest that trauma is a factor in origin The majority of writers have attributed them to yaws in general their distribution corresponds with that of yaws but there are pecial nodule foci in Brazil Africa and Indo China In 1935 only 200 cases had been reported from outside the zone of the tropics but this number has increased rapidly The cases in temperate zones show exactly the same gross and microscopic picture usually with a story of very long latent syphilitic infection Often there has been no other symptom no treatment and no recollection of infection but the blood test is strongly positive One of Liberthal s pinta cases in Chicago had juxta articular nodules

The chief difference between syphilis and yaws in respect to these nodules is their incidence Where there is widespread treponematosis childhood acquisition and absence of treatment the nodules will be present in 1 to 4 per cent of

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separately although frankly stating that it is a sequel of yaws They continue to disregard the fact that exactly the same condition occurs in syphilis, and that gangosa has no differential significance whatever between syphilis and yaws

Goundou is the African name for certain hard swellings in the malar and sub orbital regions which apparently represent an osteoperiostitis Harley [4] says it is associated with periosteal le ions elsewhere goundou and gangosa are very closely related to each other and both are undoubtedly manife tations of yaws in Liberia *Goundou however is rare or* has been reported rarely throughout the world and is not at all a constant feature of treponematous affections Cartron [2] says goundou is common on the Ivory Coast rare in the Cameroons and Guinea un known in Indo-China and Madagascar gangosa he says is common in Guam less so in Samoa rare in Cochin China and commoner in the Cameroons Goundou is probably a late sign of treponematosis and has no standing as a separate disease

Manson in his third edition (1903) speaking of nodes gummata ulcers and other late or tertiary manifestations of yaws said most recent authorities regard all such phenomena as being generally the result of an independent though con current syphilitic infection This invocation of a concomitant infection has been discarded as yaws has been established as a con titutional disease with late lesions comprising ulcers gummata aortitis sabre hins dactylitis depigmenta tions juxta articular nodules hyperkeratosis gargosa and goundou The point has been reached when it can be demonstrated that yaws and syphilis being clini cal entities of the same treponematosis partake of the same fundamental clinical and pathological character Manson says in the same place that neither disease has ever been known to change into the other This statement seems equally out of date According to the evolutionary interpretation expounded in this sec tion there have been innumerable in tances of such metamorphosis not only from nonvenereal treponematosis to venereal but also in the reverse direction

Hutchinson[11] said Frambesia cromwelliana (sivvens) is now acknowledged to have been nothing but a severe form of syphilis spreading independently of sexual intercourse *Precisely the same kind of reasons were formerly applied to* prove the non identity of sivvens and syphilis as are now employed to prove the non identity of yaws (and syphilis) It is probable that these reasons are of no more validity in the latter case than they have proved in the former Of syphiloids Hutchinson said he doubted whether it was desirable to permit the use of the word but its mere existence favored the suspicion that syphilis might receive modifications in connection with race and social habits The question as he saw it was whether there was a family of di eases of which syphilis was one — and this was the implication of the word syphiloid — or *whether they were all modifications i e patterns of one disease* [6]

In his day at the end of the last century that one disease would be called

the adult population They are exceedingly rare when treponematosis is less prevalent adult acquired and subjected to treatment Thus these nodules are another illustration of the influence of epidemiology upon the pattern of treponematosis In syphilis operating upder the same environmental conditions as yaws, e g in bejel nodules of this character are present in the adult population in the same frequency as in yaws[6]

Much of the early confusion between treponematosis and leprosy came through *gangosa* Harley[54] in Africa describes it as " visible destruction of the nose and upper lip the amount of destruction varying from infiltration with beginning ulceration of the nares to complete absence of the nose and palate, so that one may look down the patient s throat without having him open his mouth Maxwell [8] in 1839 described ulcers in nose and throat extending downward to the larynx He said that yaws and leprosy were in this respect possessed of an identity of phenomena and he concluded that the virus of yaws possessed the power of producing leprosy Leys [1] quoted Impey writing in 1896 and calling attention to the importance of recognizing antecedent or coexistent syphilis as a complicating factor in leprosy Impey placed a large number of cases under the heading of syphilitic leprosy and Leys adds that there are undoubtedly many syphilitic lepers Leys coined the term rhinopharyngitis mutilans and said it was a disease sui generis due to a specific fungus or bacterium, causing early ulcers developing from superficial grey pellicles at the back of the pharynx on uvula, palate and pillars He differentiated this from leprosy Mink and McLean [9] gave a similar description and also distinguished it from syphilis and yaws Reference has been made above to the confusion between these treponematous erosions and leprosy in early European ' syphiloids Hutchinson saw many " gangosa lesions in his personal practice with ' destruction of the epiglottis sclerosis of the larynx and now and then almost entire occlusion of the pharynx with posterior adhesions of the velum " [70]

Powell[101] in 1923 believed much of the literature describing tertiary yaws was unconvincing and thought that gangosa was due to syphilis, but others impressed by the close association with yaws coined the term ' nasopharyngeal yaws Kerr [8] in 1922 advocated removal of gangosa from the nomenclature, believing it to be yaws He noted the reciprocal frequency of raspberry yaws and gangosa in Manila compared to papulo circinate yaws and gangosa in Guam Basedow[3] said the aborigines of Australia did not discriminate between yaws and gangosa This was the condition called mentagra by the Plinys, confused with leprosy in the Middle Ages found today in vestigial European syphiloids ' in bejel in the Arab syphilis of North Africa and in the yaws of Liberia Haiti and Oceania in brief, wherever man s indifference and the environmental circumstances permit untreated juvenile treponematosis to flourish Some textbooks still list gangosa

spirochete for an ancestor The evidence that is available gives me the impression that the spirochete of either yaws or syphilis has undergone a functional but not a morphologic mutation in some human host giving rise to the other infection and that the resemblances between the two infections indicate that the new infection has evolved from the older one in comparatively recent times

1938 — Chambers Syphilis may be a biological development of yaws consequent on infection in a *completely* non immune race living under different environmental conditions

1939 — Hamlin No adequate explanation has been offered for the emergence of syphilis The evolutionary affinity of yaws and syphilis as shown by clinical pathological and immunological comparison is further emphasized by their geographic relationship Correlation of the geographical background of treponematosis with anthropological knowledge concerning the diffusion of races suggests that syphilis is the *most recent morphological* (sic) type *T pertenue* being characterized by relatively weaker serological and constitutional responses and being generally less invasive *is* phylogenetically older in its human parasitism than is *T pallidum*

1942 — Craig[8] As in the case of the spirochetes causing syphilis and yaws the two (trypanosomes) may have originated from a common root species, but at the present time differ so much in *their* virulence and manifestations that it would seem best to consider them as separate species causing distinct clinical conditions

1944 — *Fox*[1] *Yaws and syphilis are closely related diseases The morphologic* identity of the causative organisms the same serological reactions the same response to treatment and the clinical identity of the late manifestations might appear to be strong evidence that yaws and syphilis are *the same* disease However it should be pointed out that three of these four similarities exist *between* pinta and syphilis which are totally different diseases

Manson Bahr in his 11th edition[8] says that the organisms of syphilis and yaws are indistinguishable and the lesions produced by them extremely difficult to differentiate yaws is now thought to be merely a *primitive and tropical form* of syphilis Strong *in* his 7th edition[8] says Perhaps the most conservative view in this respect is that we have in yaws a modified virus of syphilis — a less virulent one producing a disease which has been modified through *many* years of successive passage of the virus through the epidermis in black skinned races by the habits of life of these people and by the climate and hygienic conditions under which they live There is *much* evidence in support of this view

syphilis rather than treponematosis He used syphilis in this inclusive sense when he said "The first step in order that we should understand syphilis, is to recognize that it is by no means necessarily a venereal disease" He lacked the useful word treponematosis and therefore could not avoid ambiguity between syphilis the venereal disease and syphilis the world disease Butler[1] in his contention for the unity of syphilis and yaws called them both syphilis, thus failing to take advantage of the useful neutral complexion of his own word treponematosis It is no longer necessary to claim that syphilis is yaws or yaws syphilis, it is sufficient to say that each is a pattern of treponematosis

Hutchinson expected yaws to follow sibbens and radesyge out of the 'syphiloids' and into the syphilis' camp "As long as sivvens radesyge and some other locally endemic maladies were held to be other than syphilis, they too were classed as 'syphiloids Yaws is indeed almost the only malady which keeps the field (of the 'syphiloids'), and as regards it the contest cannot, I think, last much longer' He was far too optimistic, greatly underestimating the strength of the static two disease concept The following opinions, selected almost at random from the literature show how much reluctance there still is to think of treponematosis in dynamic evolutionary terms If evolution is mentioned in connection with yaws and syphilis it is only to emphasize further divergence from each other or a common source

1932 — Williams[13] concluded that syphilis arose in the New World in the past 10 000 years

1933 — Harley[4] said "It is quite likely that evolution of the two diseases (or branches of some parent disease, if you will) is proceeding divergently, and that eventually we shall have two or more readily differentiable entities'

1934 — Turner and Chesney[1 3] "It is of course entirely possible that at some remote date in the past the treponemes of yaws and those of syphilis were identical and that they produced only one type of disease but of this there is no definite evidence at the present time'

1934 — Turner[1 1] Whether all of these organisms (treponemes) were derived from a common stem and if so at what period differentiation occurred can only be surmised There is no convincing evidence that differentiation first occurred within historic times for certainly yaws and syphilis have presented much the same clinical and epidemiological features over the entire period for which adequate descriptions of these diseases are available'

1935 — Williams[131] followed Manson (1903) saying that transformation from one disease to the other had never been observed "Probably all will agree that the spirochetes of yaws and syphilis originally had the same

that primitive and transitional forms of the infection were screened out and the opportunities for sexual transmission proportionately increased It required several centuries for this adult venereal disease to emerge into its present form At certain times and in certain places in Europe conditions of human life have deteriorated subsequently to such an extent that primitive and transitional forms of the infection have reappeared under the name of the ' syphiloids

In the past attempts have been made to differentiate between the most primitive forms of treponematosis known generally as yaws and the sophisticated form known as syphilis but differences between the two forms have proven upon examination to be quantitative in nature and due largely to environmental influences

This view is opposed to the view usually held It is to be noted however that both views are interpretations of the same facts The view usually advocated is held so generally and has been for so long that in the minds of many it has come to have the force of fact but this is erroneous There is no conflict as to the facts Each interpretation eventually will stand or fall on its merits

The present interpretation has three merits First it stresses etiology holding that *if two forms of disease are caused by the same parasite or by strains of* the same species they are the same disease no matter how different they seem Identity in causative agent is identity of disease In this sense treponematosis is one disease As a corollary of this position disease classification must remain subordinate to taxonomy Otherwise the cart is before the horse Zoologists *determine species by self imposed rules which definitely limit the prerogative to* create new species It may be disturbing to clinicians that zoologists should have the last word in the classification of parasitic diseases but doctors have no right to erect new species of otherwise indistinguishable organisms to match each of their clinical syndromes Yet this truth has been disregarded in respect to *T pertenue* and *T carateum* Yaws and pinta are syndromes they *are not* independent diseases because they are not caused by zoologically specific parasites

Secondly the present interpretation refuses to allow epidemiological factors to affect disease classification The fundamental part of the disease is what remains after the influence of epidemiological factors has been determined *estimated and eliminated Environment affects the immunological course of a disease* the physiological reactions of host and parasite the morphological character of the lesions and the various peculiarities in pathology Since these and other components of a disease vary with the environment it follows that so long as differences between forms of treponematosis can be accounted for on epidemiological grounds there is *no justification for using these differences to bolster a denial* of the fundamental one ness of treponematosis There is evidence to support the view that even the biological characteristics of the strains of the parasite have their origin in environmental pressures of one sort or another The functional

Holcomb in 1945[63] says, 'The treponemiases like the malarias, are a group of diseases closely related to each other They are all caused by a treponema, each of which cannot be distinguished morphologically from the other This group is at present represented by the diseases known as syphilis, yaws, bejel and pinta '

These quotations are illustrative of the wide variety of assumptions and concepts presently invoked to interpret the relationship of syphilis and yaws Perhaps it is possible to say that there is at least a tendency in the literature toward rapprochement of the two diseases although it must be admitted that this usually takes the form of consent to a common ancestor or a prehistoric identity rather than a unitarian view of treponematosis in the living present There is uncertainty whether syphilis came from yaws, or yaws from syphilis or both from a third form No one has previously developed the suggestion that metamorphosis has taken place in the past and is still going on, in either direction as circumstances of human life dispose

Summary and Conclusion

> "A problem well stated is half solved If not, omitted or forgotten points intrude as soon as discussion begins
>
> Fournier

The view presented herein is that treponematosis is a universally distributed disease caused by *Treponema*, a genus with one species *pallidum* This disease presents different clinical patterns under different climatic and sociological conditions Any variations in the parasite itself are functional in nature and represent strains, which may or may not have fixed biological characters Treponematosis is an ancient disease of man, which probably spread from an origin in Africa Black slavery brought the infection to Europe continuously over thousands of years and took a large amount of it to the New World Endemic treponematosis in Europe was compounded of infections 1) thus brought by slaves from North Africa, 2) brought back from the Near East by the Crusaders and 3) introduced by the new Portuguese slave trade with West Africa The theory of an 'epidemic' of syphilis in Europe about 1500 is not well supported The theory of the American origin of syphilis is objectionable on two grounds, 1) it assumes that syphilis is a different disease from the rest of the treponematosis in the world, and 2) it assumes not only that Columbus brought back a highly infectious venereal disease from America but that the venereal feature was as 'new' as the disease itself The venereal character of this form of treponematosis, however, was not due to its sudden importation into Furope by a shipload of explorers but rather to the gradual development in Europe of a fabric of human life so hygienic

that primitive and transitional forms of the infection were screened out and the opportunities for sexual transmission proportionately increased It required several centuries for this adult venereal disease to emerge into its present form At certain times and in certain places in Europe conditions of human life have deteriorated subsequently to such an extent that primitive and transitional forms of the infection have reappeared under the name of the syphiloids

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properties of the parasite will respond to meet the stimuli of each change in host and environment — will in fact reverse their form, if environmental conditions are reversed Functional variations in the parasite are, therefore, not valid bases for disease differentiation

Thirdly this interpretation thoroughly integrates treponematosis with the human race Primitive people in certain environments have a juvenile infection e g yaws less primitive people, where there is some civilizing influence, tend to a transitional type of infection, cleanly and civilized communities have an adult venereal infection, e g syphilis This metamorphosis is integrated with man s social evolution not only in many different places but throughout his whole history The earliest appearance of treponematosis was the juvenile, the next was the transitional type and the latest is the adult venereal disease in a sense peculiar to our present civilization This evolutionary parallelism between man and his disease is significant It means that no new treponeme ' need be invoked to explain the phenomena of treponematosis but that *Treponema pallidum* has travelled with man since history's dawn changing with him

It indicates that our thinking is becoming more rational when we look through appearances to causes when we insist on epidemiology bearing as much of the burden of disease difference as it can before we plunge for a difference in etiology and when we have faith in the orderly evolutionary processes of nature These are the three merits of the present interpretation They will not appeal to those who respect too highly the weight of orthodox opinion, those who still classify diseases on the basis of appearance rather than cause those who still use epidemiological features in their differential tables and those who with a static outlook on man and his diseases require each new pattern to have a name and a parasite of its own

The present interpretation does away with *T pertenue* and *T carateum* discards what is left of the theory of the American origin of syphilis and admits of one disease manifested in many clinical entities It is not entirely clear why treponematosis should particularly produce boomerang legs in Australia gangosa in Guam profuse cutaneous eruptions in Jamaica depigmentations in Mexico, profuse mucosal eruptions along the Euphrates and neurosyphilis in Baltimore The significant fact is not that it produces all these different signs, symptoms and syndromes and many others but that while doing so it remains fundamentally one disease in parasitic agent chronicity of course, underlying pathological reactions and response to treatment

The present interpretation differs from Butler insofar as he believed yaws to be syphilis it is believed rather that they are different clinical entities of the same disease It differs from Holcomb insofar as he believed yaws, syphilis pinta and the rest to be a group of diseases the treponemiases, it is believed they are not a

family of diseases but one disease manifesting itself in different patterns It differs from Turner and Fox insofar as they believe that differences in the parasite and in the clinical patterns justify regarding them as different diseases it is believed rather that they are due to parasites of the same species and constitute syndromes of the same disease

It is not desired to read into an author s words more than he means to convey but the italicized portion of the following quotation from Strong (118 page 442) *states in a textbook for the first time the exact position advocated herein* In view of the recent investigations in regard to pinta as Stitt has emphasized *it seems advisable to designate syphilis yaws and pinta as forms of treponematosis*

Apprehension may be expressed that this view would abrogate the use of the words syphilis yaws etc This does not at all follow This view does not consider such a course either necessary or advisable Here is where Turner s argument of usefulness receives hearty support Having acknowledged that they are forms of treponematosis clinicians can with perfect propriety continue to refer to them by their own names Phthisis is still a good word although it is now a clinical syndrome of tuberculosis and so is paratyphoid though it is more precisely salmonellosis Usefulness is a valid principle in nomenclature providing it is subservient to and does not seek to dictate the correct nomenclature of diseases

Many have found the unitarian concept of treponematosis cumbersome and superfluous Strong [18] quotes Chandler as follows Whether or not yaws was originally evolved from syphilis or vice versa or whether under suitable conditions alterations can still occur are largely academic questions Some dismiss classification and nomenclature as unimportant since all these forms of disease respond to exactly the same treatment

There are however four considerations which recommend the acceptance of treponematosis as a comprehensive world wide disease and they are of such cogency as to make the question of these relationships intensely practical The first is clarification of nomenclature by resolving several diseases into one of which they are component parts This is a normal procedure and is exemplified in other diseases such as tuberculosis plague (sylvatic and human) borreliosis (tick and louse borne) and yellow fever (jungle and urban African and American) In each case the new orientation has resulted in a better understanding of the disease

Secondly the very comprehensiveness of treponematosis tends to produce a new and less provincial attitude It can hardly be denied that syphilology is a very circumscribed branch of medicine and this may be partly due to the fact that it deals with only one segment of a disease Books such as Stokes disregard all the other treponematosis in the world In fact that author names yaws pinta

and even bejel along with relapsing fevers and Weil s disease as ' spirochetoses " giving biological false (sic) positive serological reactions, as if syphilis had a pro prietary right to the complement fixation reaction, which yaws and pinta do not share The point of view is understandable The book deals solely with syphilis, the venereal form of treponematosis as seen in a civilized country The point of view is natural, but is such myopia wise? It is urged that a wider horizon would result in a better understanding of syphilis itself If every syphilologist should spend part of his training period in Haiti or Liberia watching the reaction between the treponeme and primitive man, he would gain a valuable breadth of view for his work with the treponeme and civilized man, providing he were free from the preconception that yaws is an exotic disease caused by a different parasite

Thirdly research in treponematosis is now handicapped by compartmental thinking The assumption that yaws and syphilis are different diseases is a bar rier to any comprehensive program Yaws has much to offer as a field for the study of the ecology and biology of the treponeme The pathology of trep onematosis is a unit much will be lost so long as it is studied piecemeal

Lastly, if treponematosis is a disease of all mankind, it should be recognized as such by epidemiologists, health officers, sociologists, social hygienists and civil governments Questions of sanitation, social habits, economics and laws are in volved The education of the native to live more hygienically and the education of the civilized man to solution of his sexual maladjustments are parts of the same problem The different educational procedures should be integrated It is an illusion to hope for a syphilis free civilization, while yaws remains rampant in wide areas of the world As Christian [4] says, Regions in which yaws is endemic must be considered as so many reservoirs of world infection, exactly as are foci of malaria and yellow fever "

Most doctors have a very hazy conception of yaws, and nonvenereal syphilis is a medical curiosity the layman is even less prepared to take a world view of treponematosis For both syphilis and sex are indissolubly linked they do not know that this is only half the story The other half is that the same disease under other names runs riot through great regions of the earth as a childhood disease without reference to sex Much present social hygiene material is only half true because it deals with only a fraction of a disease The public should be taught the evolutionary history of the disease how primitive man domesticated the spirochete and thereby escaped the worst results of the infection, how in civilized countries the venereal form attacks only one tenth instead of the whole population how domestication has been lost and how that has worsened the sequels of the disease The public should realize that civilized man through the use of soap and personal cleanliness has made impossible the childhood propaga tion of syphilis but that through sexual promiscuity and marital maladjustments

the door has been left open for the treponeme to attack at the most vulnerable point the reproductive age and the parasite enters through the genitalia because that is the only way left for it in a clothed and clean population In a sense syphilis is an unwelcome by product of civilization s ascent to higher levels of hygiene

This knowledge encourages a more objective attitude toward syphilis The world view of treponematosis in its medical sociological geographical and historical perspective is satisfying to the intelligence and psychologically sound Fuller use should be made of it in anti syphilis propaganda As Fournier said a problem well stated is half solved The welfare of mankind demands a solution of this problem let it be fully and honestly stated

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CHAPTER XXVIII

SYPHILIS

By FRANK W. REYNOLDS

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December 1945

INCIDENCE AND PREVALENCE

Because of the moral stigma still pertaining to venereal infections the incidence of syphilis is difficult to ascertain with any degree of accuracy As to its prevalence one of the most frequently quoted estimates is that syphilis strikes one in ten adults in the United States[1] Among selectees in World War II serological evidence of syphilis was found in 4 53 per cent of those tested there being marked geographical and racial differences To an extraordinary degree syphilis in the United States is primarily a negro problem[2]

Throughout the world the disease is more frequent in urban (especially seaport) communities than in rural areas Its prevalence can be correlated with the economic security and sexual promiscuity of the individuals of almost any community

THE ETIOLOGICAL AGENT

The *Treponema pallidum* is a delicate cork screw shaped member of the genus *Spirochaeta* It does not stain well but may be identified readily by dark field microscopy Only man normally is susceptible to infection with this organism Animal reservoirs of infection are not known to exist nor are there any known intermediary hosts Under experimental conditions certain laboratory animals may be infected In rabbits and certain primates a disease not unlike the human infection follows inoculation In the mouse and some other rodents treponemes survive but no lesions become manifest

Unlike the tubercle bacillus and certain spore bearing anaerobes *T pallidum* dies as soon as it dries Owing to this fact the organism is *transmitted from one person to another by direct or indirect contact* of the moist surfaces of the body most often the genitalia and the buccal mucosa It is killed readily by many chemicals and by heat In vitro relatively low concentrations of soap solution and of many antiseptics suffice to destroy it On the other hand the organism is extremely resistant to low temperatures Rapidly frozen and stored at 76 C it remains viable and pathogenic for many years[3] In the tissues of man or experimental animals the treponeme lives for years and unless destroyed by treatment may persist throughout the life of the infected host

It is probable that *T pallidum* reproduces by transverse fission It has been suggested although not proved that in addition to the familiar spiral form of the organism there exists a granular form which likewise

Definition —Syphilis is a specific infectious disease, acute in its early phase but exquisitely chronic in its many late effects It is an infection with certain characteristic manifestations but which in its protean effects may closely simulate a vast array of other clinical entities Most often disseminated in venery, the disease also may be acquired innocently or transmitted by a syphilitic mother to her unborn child Because of its prevalence, its contagiousness during the early stages and the seriousness of its late complications, syphilis constitutes one of the most important as well as one of the most remarkable diseases of man

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It is probable that *T pallidum* reproduces by transverse fission It has been suggested although not proved that in addition to the familiar spiral form of the organism there exists a granular form which likewise

is virulent Those who hypothesize the existence of granular forms also believe that the organism may progress through a definite life cycle Whether *T pallidum* undergoes cyclic changes, which include forms other than spiral, can be neither substantiated nor categorically denied on the basis of present information

It is suggested by clinical observations of the frequency of conjugal neurosyphilis and of the development of neurosyphilis in several individuals infected from a common source that there may be strains of *T pallidum* which have an affinity for certain tissues In experimental animals cross immunization studies appear to indicate the existence of heterologous strains (similar data are not available for man) Whether these strains also differ in their affinity for the nervous system or other tissues is unknown, since in no laboratory animal is the neuraxis damaged

Despite the early claims of Noguchi[4] *T pallidum* has not yet been successfully cultivated on artificial media in a form virulent for experimental animals or man Were it possible to grow pathogenic organisms, many of the unsolved problems of syphilology could be subjected to laboratory study

The Course of Untreated Syphilis

Mode of Infection—Although an abrasion of the skin or mucous membranes greatly facilitates entry of the treponeme into a new host this is not always necessary, for in experimental animals it appears to penetrate intact mucous membranes[5] On exposed surfaces of the skin some abrasion probably is essential, since otherwise the organism may die by desiccation before it can penetrate the thick, dry layers of the epidermis Infection also may occur by inoculation directly into the blood stream as in transfusion accidents and in congenital syphilis

Dissemination of Organisms—Having entered a new host, the treponemes of syphilis find a medium suitable for multiplication and spread As motile organisms, they enter the lymphatic channels and within a few hours have penetrated as far as the regional lymph nodes Here they multiply and spread further by way of the efferent lymphatics until they reach the blood stream They have been demonstrated in the blood of both animals and man weeks before the appearance of the primary lesion

By the blood stream treponemes are carried to all tissues of the body Here, as in the Biblical parable, some of the organisms fall upon barren ground unsuitable for growth and multiplication, others find local condi

tions favorable especially those that lodge in the skin and mucous membranes the eye and the cardiovascular and central nervous systems The foundation for all of the late manifestations of syphilis probably is laid at the time of the early treponematemia

Symptomless Infection — Although in most instances infection with *T pallidum* is followed by a visible tissue reaction at the portal of entry and although the dissemination of the organisms usually is followed by a generalized tissue reaction either or both of these phenomena may fail to occur Infection may take place without any demonstrable lesions

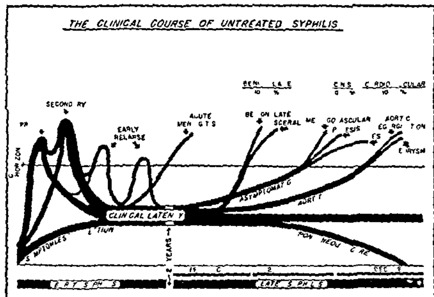


Fig 1 Diagramatic schema of the clinical course of untreated syphilis

The precise mechanism operating to suppress the visible early reaction to infection is not well understood It may depend on one or a combination of many factors such as size of the inoculum site of inoculation age of the patient or the hormonal influences of sex or pregnancy

The importance of detecting symptomless infection cannot be overestimated Since its presence is not suggested by clinical signs or symptoms it passes unrecognized until late manifestations of the disease occur unless routine serological tests are performed

Early Tissue Reaction — Approximately three weeks after the treponeme has gained entrance into a new host there develops at the portal

of entry a primary lesion, the chancre. For several days this enlarges and is followed by a painless swelling of the regional lymph nodes that drain the chancre site. After about 6 weeks, when the chancre is beginning to involute spontaneously, generalized lesions of the secondary stage appear on the skin and mucosal surfaces. There then may occur mild or moderate evidences of a constitutional reaction. These persist for a variable period of time, ranging from a few days to several months and in their turn disappear spontaneously. The early lesions of syphilis are characterized by a relatively mild tissue reaction to an enormous number of organisms. The lesions are superficial, do not destroy tissue and usually heal without scarring. With healing the organisms largely disappear from the skin and mucous surfaces.

Latency.—Following the spontaneous healing of the early lesions there ensues a period during which outward signs of syphilis are conspicuously absent, and during which the infected individual is recognizable as syphilitic only by means of blood serological tests. This period of latency may persist for a few months or may be prolonged throughout life. It is as if the invading organisms and the infected host had reached a truce and agreed to live together peaceably. During the first two years of the latent period, and rarely thereafter, the armistice may be broken by one or more periods of spirochetal aggressiveness during which infectious relapsing lesions occur on the skin or mucous membranes.

The latent period may be divided conveniently into two parts, early and late, with the dividing line drawn arbitrarily two years after infection. During early latency infectious relapse constantly threatens to break the outward tranquillity. Later, the menace of renewed infectiousness is largely removed, but as the disease becomes converted from a generalized infection to a focal disease, late complications of the disease may develop at any time.

Late Tissue Reaction.—During the variable period of latency three phenomena may be taking place beneath the outwardly serene surface. First, all anatomic evidence of infection may disappear, so that at necropsy, when the patient finally dies from some other cause, all evidence of syphilis is conspicuous by its absence. Next, the reaction of the host toward the invading organism may be altered, the tissues apparently becoming sensitized, and instead of superficial, insignificant lesions rich in treponemes he develops with explosive violence large destructive lesions, gummas, which contain relatively few organisms. Third, there may be a slowly progressive, exquisitely chronic and insidious inflammation in various tissues, particularly in the cardiovascular and the nervous

systems, with subsequent fibrosis and ultimate impairment of physiological function

The gummatous process which underlies most of the lesions of benign late syphilis usually is the first of the late manifestations to appear The incubation period of neurosyphilis varies with the type but in general clinical evidence of such involvement is most common in the second and third decades of the disease Cardiovascular lesions become manifest still more slowly their incidence reaching an acme early in the third decade following infection

Precocious Tertiarism—In rare instances for reasons imperfectly understood the entire course of syphilitic infection is accelerated so that the patient develops early and sometimes even simultaneously with typical early manifestations lesions characteristic of the late stage of the disease

Pathological Anatomy

The reaction of the body tissue to the treponeme of syphilis is characteristic and histologically the lesion is the same[6] no matter what structure is affected nor in what stage of the disease it appears This lesion is a granuloma having its origin in the perivascular lymph spaces and consisting of a cellular infiltration about the small vessels composed of proliferated fixed connective tissue cells lymphocytes and plasma cells The infiltration at first surrounds the vessel in characteristic coat sleeve form but later becomes more extensive and diffuse The endothelial cells of the capillaries are swollen and proliferated narrowing or occluding the lumina of the capillaries usually also there is a formation of new capillaries Giant cells are seen occasionally

The growth of the process is centrifugal the more recent cellular infiltration showing at the periphery and the earlier retrogressive changes appearing at the center Gradually the new connective tissues cells are converted into fibrous tissue and the process becomes sclerotic or the central portion of the lesion may undergo degeneration, caseous fatty or mucoid and if near the surface may break down and ulcerate

In the primary lesion or chancre the changes just described involve chiefly the cutis The secondary stage of the disease is marked by eruptions upon the skin and mucous membranes In the macular syphilid there is dilatation of the superficial vessels of the skin with a slight cellular infiltration with lymphocytes and plasma cells about them In papular syphilids the characteristic infiltration with lymphocytes

plasma cells and fibroblasts involves the cutis and projects above the surrounding skin In certain syphilids the circumscribed infiltration bears a special relation to the hair follicles and the sebaceous glands and ducts The extension of serpiginous syphilids probably is due to a progressive thrombosis of the vessels In condylomata lata the outstanding feature is the marked papillomatous overgrowth Pustular syphilids are believed to be the result of a secondary pyogenic infection, especially of the hair follicles or the sebaceous glands Most of the secondary syphilids show a marked tendency toward complete resolution and absorption

The characteristic manifestation of the late or tertiary period of syphilis is the gumma The lesion is a typical granuloma, differing from the lesions of the primary and secondary stages in its tendency to grow to large size and especially in its proneness to undergo degeneration and softening This latter peculiarity depends upon a state of hypersusceptibility of the tissues themselves rather than upon any increase in the virulence of the organisms Degenerative changes begin in the center and extend peripherally The accumulated cells and the connective tissue undergo necrosis and form an area of degeneration, which usually is caseous but which may be chiefly fatty or mucoid If near the surface the gummatous area usually ulcerates In the deeper tissues the peripheral part of the lesion gradually is transformed into connective tissue the central degenerated area ultimately may become absorbed and the whole mass may be converted into dense fibrous tissue Seldom is it possible to demonstrate treponemes in these late lesions, whether by dark field examination or by tissue stains

Few pathologists now accept Warthin s conclusions[7] regarding the frequency and specificity of diffuse, infiltrative lesions throughout the various viscera (heart, pancreas adrenals liver testes) as pathognomonic of infection with syphilis Indeed only in the aorta do miliary gummas[8] appear to occur with any great frequency In other organs the Warthin lesion is non-specific and as Rosahn and Black Schaffer[9] clearly show in their carefully studied material more closely related to the aging process than to infectious disease

Immunity to Syphilis

The reaction of the host to infection with syphilis is neither as dramatic nor as complete as is the case with certain other infectious diseases Nevertheless there is developed a state of immunity sufficiently

powerful to allow spontaneous healing of the early manifestations and to induce clinical latency. In addition, as previously indicated, the immune reaction may be sufficient to maintain a peaceable status quo between host and parasite throughout the life of the host or even powerful enough completely to rid the host of the invaders. Immunity in syphilis seems to be predominately cellular[9] although humoral antibodies with at least some protective value can be demonstrated by appropriate techniques[10]

Thus far attempts to produce in man or in experimental animals an effective immunity to syphilis by the utilization of derivatives of syphilitic tissue or cultures of (non virulent) spirochetes have been uniformly unsuccessful[11] Attempts to confer immunity by passive transfer of serum from immune persons or animals likewise have been fruitless

Natural Immunity

There is no natural immunity to syphilis in man. Any human being exposed often and intimately enough will acquire the infection

Acquired Immunity

It is convenient to divide this discussion into two parts (1) the resistance of the infected individual to organisms freshly introduced from without, i e his susceptibility to reinfection or superinfection and (2) his resistance to the noxious effects of the organisms present in his own tissues

Resistance to Reinfection or Superinfection.—The evolution of the immune state requires time. If deliberate reinoculation is practiced on an already infected but untreated experimental animal or man the second inoculation usually results in a chancre only if it is carried out early. Later no lesion at all ordinarily follows reinoculation. In animals it is possible to overcome this refractory state and to produce a true superinfection by such a drastic procedure as intravenous reinoculation. In humans a few cases of probable superinfection have been reported

In man reinfection can be recognized incontrovertibly only when a second chancre develops. While symptomless or d emblee reinfection may and probably does exist in man its occurrence cannot be proved. The vast majority of the reported reinfections in man have occurred in patients who had received intensive treatment during the first six months of their original infection[1]

The refractory state against a second inoculation then is essentially similar in animals and in man In treated early syphilis reinfection may occur in treated late syphilis it is practically unknown The situation with respect to adequate early treatment seems clear, the development of the immune response is aborted by complete destruction of all the treponemes in the body When treatment is given later, after immunity has been established and the infection has become latent, the state of affairs is less well understood Chesney[9] maintains that the immune state, once fully established, is not dissipated by treatment, even though all the organisms have been destroyed Other investigators, notably Neisser[13], have been unwilling to concede that complete sterilization has been effected and contend that persistent immunity implies persistent foci of infection Most often the treponemes of the second inoculation are not disseminated but are destroyed in situ by the immune mechanisms of the host[14]

Resistance of the Individual to Treponemes Present in His Own Tissues—The fact that resistance to syphilitic infection actually does develop is demonstrated not only by the development of the refractory state to reinfection but also by the evolution of the untreated disease The early lesions heal spontaneously and if one repeatedly examines accessible healing lesions with the aid of the dark field microscope treponemes are found to be rapidly declining in numbers Some change has taken place in the tissues of the host which makes them less favorable sites for multiplication of the organisms There comes to be established an equilibrium between the treponeme and the defense mechanism of the host so delicately balanced that relatively minor changes may turn the tide to favor either host or parasite

Of the many factors[1], which may influence the outcome of the interaction between invading organism and the host during the quiescent or latent period of the infection there is good clinical or experimental evidence for but five, (1) the character and extent of the early tissue reaction (2) trauma (3) sex (4) pregnancy and (5) the race of the host

Both in animals and human beings there is evidence that the more extensive the *early tissue reaction*, the less likely is the individual to develop serious late manifestations of the disease In man the central nervous system appears particularly to partake of this protection Parenchymatous neurosyphilis is rare in patients whose secondary lesions were extensive common in those whose early reactions were trivial or nonexistent Furthermore, in man the development of 'allergy" in the form of gummatous lesions may confer some protection on the nervous

system and perhaps on the cardiovascular system as well What proportion of this protection' is due to the fact that patients with obvious skin lesions are more likely to receive antisyphilitic treatment than are others is not known

The effect of *trauma* is deleterious to the host Tissue, which has been injured offers a favorable site for the rejuvenation and multiplication of quiescent treponemes, perhaps by interference with local tissue immunity It is not uncommon to see the development of early or late lesions in superficial injuries of the skin, e g tattoos or in fractures or lesser injuries of bone *The sex of the host materially modifies the course* of syphilis since the infection is much milder in women than in men The influence of *race* on syphilitic infection is most clear cut between negroes and whites Negroes are particularly prone to develop lesions of the bones and cardiovascular system white patients to develop lesions of the central nervous system[16]

Syphilis Immunity and Reagin Formation

Closely paralleling the development of immunity to syphilitic infection, there appears in the blood serum and certain tissue fluids a substance as yet unidentified called *reagin* The origin of reagin is questionable Whether it is a product of the disintegration of the bodies of dead spirochetes results from the interaction of living spirochetes with certain tissue cells or is perhaps a combination of both is not known

Despite the fact that reagin formation parallels in time the development of the resistant state there is no definite proof that it is a *measure of the degree of immunity* Unlike immune antibodies passive transfer of reagin affords no protection against infection in experimental animals Nor is the resistant state dependent upon the presence of reagin in the blood Of greatest practical importance are the facts that reagin behaves in vitro like a true antibody which makes for its ready indentification by flocculation or complement fixation tests and that its presence in the blood is highly, although by no means completely specific for the diagnosis of syphilis

Clinical Course

Ricord s classic division of the clinical course of syphilis into three phases primary secondary and tertiary had done much to facilitate a clear understanding of the disease It is important to bear in mind

however, that these stages often are by no means sharply defined, that they frequently overlap, and that the actual progress of the disease is continuous and uninterrupted, even though its outward manifestations may be intermittent or occasional In many respects, syphilis is two diseases in one, the first, early syphilis, acute and infectious and similar in many ways to the eruptive fevers, the second, late syphilis, a chronic inflammatory disease which may involve almost any portion of the human body, but with especial predilection for certain organs and structures

Early Syphilis

The Primary Stage

Following a period of incubation, which varies from two to six weeks but is most commonly between three and four, the initial lesion, chancre, appears at the site of inoculation This is usually upon the genitalia but may be upon any part of the skin or the accessible mucous membranes In rare instances syphilitic infection has been known to occur without the primary lesion, syphilis d emblee

Extragenital chancres[17] in general have many of the characteristics of genital chancres but are apt to be somewhat larger in size, and, on the finger at least, they may be quite painful The commonest site of the extragenital chancre is the lip, the infection resulting from the act of kissing Physicians and dentists may be infected on the finger or hand in examining syphilitic patients A syphilitic infant may infect its wet nurse, or a syphilitic nurse may transmit the disease to a healthy infant On rare occasions the disease may occur from the use of contaminated objects such as drinking glasses, eating utensils towels and so forth

Blood serological tests cannot be relied upon in primary syphilis, since the appearance of the chancre usually precedes the elaboration of sufficient reagin to be detectable by serological tests It is feasible to sub divide primary syphilis into sero negative and sero-positive stages the former merging into the latter at various time intervals in different patients It should also be noted that other genito-infectious diseases chancroid, lymphogranuloma venereum, may be associated with bio logically, false positive serological tests for syphilis[18]

The Secondary Stage

At first syphilis produces no marked constitutional reaction Be neath the outwardly serene surface, however, treponemes have been

widely disseminated throughout the body and are still actively multiplying in their many sites of implantation After a period of from four to twelve weeks following the appearance of the chancre the clinical picture rather abruptly changes to one of an acute systemic infection with generalized eruptions on the skin and mucous membranes and a variety of other manifestations

Cutaneous Lesions—It is not within the scope of this system to attempt a detailed consideration of the many cutaneous lesions of early syphilis which are extraordinarily diverse in their appearance and characteristics and which resemble those of a great variety of other conditions They possess however certain general characteristics which aid in their recognition and in distinguishing them from these latter

Some of the most significant characteristics of early syphilids are the widespread and symmetric distribution of the lesions their polymorphism the tendency of some to be arranged in circles and segments of circles the usual absence of subjective symptoms such as pruritus and pain and their ready response to antisyphilitic therapy The individual lesions usually are small In white patients they are commonly pink or coppery in color in negroes reddish brown or tan Most syphilids heal without scarring although at times there are residual areas of localized atrophy of the dermis macular atrophy

Mucosal Lesions—Mucosal lesions may occur in conjunction with skin eruption or as the only manifestation of secondary syphilis The limitation of secondary lesions to mucosal surfaces occurs more frequently in negroes and in females

Lesions of the oral or genital mucous membranes may occur as (1) diffuse erythema ( ) simple erosions (3) papulo erosions (mucous patches) (4) papulo hypertrophic lesions (condylomata lata) These lesions are especially important because of their highly contagious nature

An erythema of the tonsils soft palate uvula and pharynx with sharply defined anterior borders is a common and characteristic manifestation of secondary syphilis Simple erosions appear as small round or oval areas denuded of epithelium resembling the superficial erosions which result from lip biting Mucous patches the most frequent mucosal lesion in early syphilis are indolent maculopapular lesions modified by their location on moist surfaces and superficially ulcerated The eroded surface is covered by a pale greyish membrane Seldom is there any significant inflammatory areola

Condylomata lata are papular lesions modified by their situation in moist areas and by the presence of filth and irritating discharges They

are more common in negroes than whites and occur in females more often than males The most frequent site is upon the genital and anal mucous membranes but they also occur in other moist areas such as in the axilla beneath the female breast and between the toes Condylomata acuminata (venereal warts), multiple chancroidal lesions and ecthyma must be differentiated

General Symptoms of Secondary Syphilis

Despite the widespread tissue reaction and the presence of enormous numbers of treponemes, few patients with secondary syphilis feel acutely ill Many develop low grade fever of which they may not be aware Malaise, anorexia, slight weight loss, headache and rheumatic pains are not infrequent Severe constitutional reactions are most common in patients with pustular eruptions Here, chills, high fever (104 F), nausea and vomiting may become manifest

Lymphadenopathy—A characteristic feature of secondary syphilis is generalized enlargement of the superficial lymph nodes Usually this appears coincidentally with other systemic disturbances but rarely it may be the only clinical manifestation The nodes are discrete, rubbery and non-tender They are likely to be symmetric in distribution and are the expression of the general infection rather than the result of any local lesions of the skin or scalp The nodes most constantly involved are the post auricular, sub occipital submaxillary, the sternomastoid chain axillary, epitrochlear and inguinal In negroes lymphadenopathy may be so marked as to stimulate primary diseases of the lymphatic system

Alopecia—Although alopecia accompanying secondary syphilis may be due to lesions in the scalp, these usually are not present Characteristically there is a patchy, "moth eaten , loss of hair, most marked about the margin of the scalp and more obvious in males because of their shorter hair The loss of hair is not limited to the scalp, the eyebrows, beard or body hair occasionally are involved The alopecia is not permanent, hair regrows with the passing of the secondary stage

Ocular Lesions—*Iritis*, the most common ocular lesion of early syphilis occurs in about 4 per cent of all untreated cases of secondary syphilis and is even more frequent as a relapse after inadequate treatment Syphilitic iritis occurs in two forms The common type differs in no way from iritis due to other causes The usual subjective symptoms pain lacrimation, photophobia and dimness of vision, are present The

objective manifestations are circumcorneal injection and inflammatory changes in the iris itself Posterior synechiae are not infrequent and secondary glaucoma may occur The second type is the so called iritis papulosa This a rare but characteristic lesion consists of minute yellowish red nodules distributed over the surface of the iris

Optic neuritis is not uncommon in early syphilis The clinical picture is haziness or obliteration of the normal neuroretinal outlines blurring or loss of the physiological cup and edema and hyperemia of the nerve head In severe cases the inflammation may spread from the nerve to the adjacent retina producing a picture of *neuroretinitis* Like iritis early syphilitic optic neuritis may occur in association with untreated secondary syphilis or as a relapse after inadequate treatment like iritis also it cannot be differentiated clinically from optic neuritis due to other causes The response of both to antisyphilitic therapy is prompt and satisfactory

Skeletal Lesions —Pains in the bones and joints are common in early syphilis Osteocopic pains in the long bones and polyarticular arthralgia are characteristically worse at night Most often these are not attended by demonstrable skeletal abnormalities Acute *periostitis* is not infrequent Any portion of the skeleton may be affected but the skull and tibiae are the most frequent sites of involvement Palpation reveals a tender localized swelling which produces no roentgenographic changes More rarely destructive osseous lesions[19] *osteoperiostitis, osteomyelitis,* occur producing punched out osteolytic changes which can be demonstrated by x ray examination

Syphilitic arthralgia, characterized by migratory rheumatic pains affects chiefly the larger joints Arthritis with *hydrarthrosis* occurs and from the synovial fluid *T pallidum* has been demonstrated by animal inoculation[20]

Visceral Lesions —In view of the hematogenous dissemination of treponemes throughout the body tissues it is surprising that seldom are there detectable visceral lesions in patients with early syphilis

Syphilitic *nephrosis*[21] the most frequently encountered of these manifestations differs clinically from other acute nephroses only in its prompt response to antisyphilitic treatment Acute *hepatitis* is alleged to occur in early syphilis either in association with other secondary manifestations or perhaps as the only evidence of clinical relapse Its clinical characteristics hepatomegaly with painless jaundice are not distinctive Involvement of the gastrointestinal tract is even more rare although superficial and interstitial gastritis both have been described[3]

Blood Serological Tests in Secondary Syphilis—With modern serological techniques positive reactions to flocculation and complement fixation tests are almost invariably found in patients with secondary syphilis Rarely a prozone reaction may obscure the presence of syphilitic reagin Even more rarely one encounters a patient who fails to elaborate detectable amounts of reagin in the presence of overt secondary manifestation

Relapsing Early Syphilis

Untreated or inadequately treated, syphilis is a chronic disease of multiple relapses occurring both early and late in the course of the disease In early syphilis relapsing lesions commonly involve tissues of ectodermal origin, the skin and mucous membranes, the central nervous system and the eye Rarely skeletal or hepatic involvement occurs as a phenomenon of relapsing early syphilis

Infectious Mucocutaneous Relapse—Most patients with early syphilis, untreated or inadequately treated, are, for a period of months or even years subject to recurring lesions of the skin and mucous membranes With the passage of time developing immunity finally suppresses these recurrent manifestations

The lesions themselves often are trivial, usually asymptomatic and frequently unnoticed With each relapse the lesions become fewer in number and tend more and more to assume the clinical characteristics of late syphilids From the epidemiological viewpoint they are of great importance because of their infectiousness

The majority of infectious relapses occur within the first six months nearly all will have occurred by the end of two years[21] Occasionally relapsing lesions are observed between the second and fifth year but after that they are extremely rare The time of occurrence of relapse after inadequate treatment is related to the character and intensity of that treatment In general the less prolonged the course of therapy, the earlier will the majority of relapses occur

Neurorecurrence—Of more serious import to the individual but less important epidemiologically is the neurorecurrence which may be either symptomatic or asymptomatic The symptomatic form is manifest as *acute syphilitic meningitis*, rare in untreated early syphilis but more frequent after inadequate therapy

Ocular Relapse—The lesions of ocular relapse are similar to those occurring in secondary syphilis Most freqently they are manifest as

Table I The Relative Frequency of Various Types of Early Relapse (after Turner[16])

Type of Early Relapse	Per cent
Infectious mucocutaneous relapse	6
Neurorecurrence	26
Ocular recurrence	10
Other recurrent lesions	
TOTAL	100

iritis or optic neuritis The frequency of relapsing lesions of the eye or central nervous system is believed to be due to the fact that antisyphilitic drugs penetrate these tissues less well than they do others Hence in these sites there may be local multiplication of treponemes

Serological Relapse – The concept of serological relapse implies either that serological tests for syphilis having become negative revert to positive or that quantitative tests following an initial decrease in titer following therapy again show increasing amounts of reagin Serological relapse in early syphilis if confirmed and provided that technical fluctuations in the serological laboratory can be excluded is of serious import since it usually precedes and portends clinical relapse

Latent Syphilis

Latent syphilis is that period during which no symptoms or physical signs are clinically detectable and the patient is recognized as syphilitic only by means of positive blood serological tests Latent syphilis (Latin *latere*, to lie hidden) is occult syphilis Clinically the infection is dormant but actually it is smouldering beneath the outwardly serene surface a continuous struggle for supremacy between the defense mechanisms of the host and the aggressiveness of the invading spirochetes

All syphilitic infections are latent at some time The arbitrary division of the asymptomatic period into early less than two years and late latency is justifiable because of differences in potential infectiousness and probabilities for the achievement of serological negativity following adequate therapy

The clinical diagnosis of latent syphilis is established when a thorough physical examination, including especially the cardiovascular system the nervous system and the organs of special sense, reveals no evidence of the disease, and when the diagnosis is based either on serological tests, or if these be negative on a clear cut history of the disease with inadequate therapy or on the birth of a syphilitic child All patients with abnormal spinal fluids should be excluded from the category of latency

It is essential that false positive serological tests for syphilis be excluded The possibility of technical laboratory error may be eliminated by repetition of the tests especially if the confirmatory tests are performed by different techniques and in various laboratories Biological false positive serological reactions, which may be due to a variety of causes must be ruled out by appropriate procedures There is at present no reliable "verification" procedure to differentiate positive serological tests due to syphilis from those due to other causes Recent advances have followed two general lines the development of purer antigens and the study of techniques to differentiate syphilitic reagin from that elaborated in the presence of other conditions Tests performed with cardiolipin antigens [6] and those utilizing serum protein fractionation ultimately may prove helpful although all serological tests for syphilis must be considered non-specific until antigens made from pathogenic *T pallida* become available

The practical importance of recognizing latent syphilis is evident when it is realized that in patients, who ultimately develop serious late manifestations, the disease has passed through a period of apparently innocuous latency There is ample evidence that suitable therapy administered during the latent period will afford protection against the development of late complications

Biological false positive serological tests for syphilis [8 9] are common in leprosy malaria in its acute stages, infectious mononucleosis vaccinia rat-bite fever due to *Spirillum minus*, relapsing fever and certain types of atypical pneumonia There is no valid evidence that these tests are significantly affected by pregnancy menstruation scarlet fever jaundice subacute bacterial endocarditis tuberculosis or hyperproteinemia despite some reports to the contrary Inadequate but suggestive data are available on measles mumps varicella lupus erythematosis and other diseases most of which are characterized by some degree of fever

Late Syphilis

The essential difference between the lesions of early and late syphilis is that the former represents a widespread but superficial tissue response to an enormous number of treponemes whereas the latter consists of a localized low grade inflammatory response with tissue destruction to the presence of relatively few organisms. The patient seems to have been sensitized to the virus in his tissues, a phenomenon familiar in other infectious diseases as allergy.

The "allergic" state of the human body toward *T. pallida* does not develop suddenly but evolves gradually. There can be therefore no sharp dividing line between early and late syphilis. With the passage of time syphilitic lesions become less diffuse and more destructive.

The late manifestations of syphilitic infection which involve the skin, mucous membranes or the body skeleton have been designated as benign late syphilis. These lesions may be painful, deforming or even crippling but do not in themselves result in death of the patient. They appear most often within the first decade of the infection[30]

Late Cutaneous Lesions

The physical characteristics of most late syphilids are distinctive (Table II). When certain combinations are present the trained physician can establish the diagnosis without the aid of a serological test.

Table II. The Characteristics of Late Syphilids (modified from Stokes[31])

1. *Solitary character.* In contrast to the multiplicity of lesions in early syphilis late mucocutaneous syphilids occur as single lesions or as a few groups of lesions.
2. *Asymmetry.* Whereas the distribution of early syphilids is widespread and symmetrical, in late syphilis the lesions ordinarily occur in a limited area, rarely exhibiting bilateral symmetry.
3. *Induration.* The infiltration of the lesion, representing the accumulation of chronic inflammatory tissue, can be appreciated readily by the palpating finger.
4. *Indolence.* The late tissue reaction is one of low grade inflammation so chronic that the only cardinal manifestation of inflammation is swelling. Local heat, reddening, and pain rarely are present.
5. *Tissue destruction.* The tendency to central necrosis and ulceration is marked, more so with larger gummas than with the smaller nodular

lesions Even when ulceration is not manifest, tissue destruction is taking place beneath the surface

6 *Sharp margination* The margins of the late lesion whether gumma or nodular syphilid usually are visibly and palpably demarcated from the surrounding normal tissue This sharp margination applies also to the borders of ulcerated lesions the edges of which are punched out rather than ragged or undermined

7 *Peripheral extension with central or one sided healing* Extension of the lesion is from the periphery, and even while spread is occuring healing may be noted toward the center With gumma, healing most frequently is one-sided, with the nodular syphilid, central

8 *Circinate or arciform configuration* As a result of peripheral extension and central or one sided healing and also from confluence of lesions the advancing border of the lesion tends to form circles or segments of circles The arciform configuration is characteristic not only of the gumma or nodular lesion but also of groups of lesions of either type

9 *Scar formation* The lesions of late mucocutaneous syphilis heal with scar formation the configuration of which retains the shape of the original lesion The scar is thin, atrophic and noncontractile Recurrent lesions do not appear in the scar, an important differential point in ruling out certain tuberculids

10 *Peripheral hyperpigmentation* The lesions and scars of late syphilids frequently show a band of peripheral hyperpigmentation The pigmentation surrounding stasis ulcers tends to be more extensive than that associated with gummatous lesions

The cutaneous manifestations of late syphilis may be classified according to size as (1) gumma or (2) nodular syphilid This differentiation is one of gross morphology, since the histopathological appearance is identical Further classification depends upon the presence or absence of ulceration and upon changes in the appearance of the lesions as modified by their location

Gumma —The gumma is the classical lesion of late cutaneous syphilis, since it most often demonstrates all of the basic characteristics of late syphilids It starts as a small, round, painless, cutaneous or subcutaneous nodule Later the overlying skin becomes adherent and chronically inflamed Central softening occurs, and with ulceration of the skin a thick gummy material, which gives the lesion its name, exudes When fully developed, the gumma is a deep, punched out ulcer with an indurated base Most often it is solitary, but at times several may be present, in which case they may coalesce to form irregular, arciform

ulcerations The gumma ordinarily is not a painful lesion, but pain may be present, when the ulceration or its resultant scar impinges upon a large nerve or when there is involvement of the underlying periosteum By blocking the venous and lymphatic flow an extensive gumma may cause edema especially in the lower extremities

Nodular Syphilid —The primary lesion of the nodular syphilid is a small painless nodule, reddish in color, slightly elevated and palpably indurated Isolated nodules appear most frequently on the face especially about the nose, lips and chin More often, particularly when located elsewhere on the body the lesion consists of groups of nodules the grouped nodular syphilid which may coalesce and involve a large area A clinical variant of the grouped nodular lesion is the serpiginous nodular syphilid produced when the area involved by the nodular lesions is in the form of an irregular band

Nodulo squamous Syphilids of the Palms and Soles —Late syphilids of the palms and soles are fundamentally like other nodular manifestations of the disease but because of the thickness of the skin the nodules are flat scaly and hyperkeratotic, ulceration is rare Induration and the polycyclic arciform shape usually are retained The border of the lesion has a distinctively elevated ridge

Late Mucosal Lesions

Late syphilitic lesions of the oral mucous membranes are not uncommon The soft palate pharyngeal fauces and tongue particularly are affected, mucous surfaces of the lips cheeks and gums usually are spared

With gummas of the soft palate and tonsillar fossae tissue destruction and ulceration occur with great rapidity and pain dysphagia and fever may be marked Any destructive ulceration in these locations should be suspected of being syphilitic and serological tests always should be performed In the differential diagnosis ulcerations due to Vincent's infection (lesion more acute with characteristic gangrenous odor and Vincent's organisms by darkfield or stained smear) tuberculosis (lesion more chronic slow growing painful associated with pulmonary tuberculosis acid fast bacilli in sputum) and malignant neoplasm must be excluded If neoplasm is suspected biopsy must be carried out before therapeutic tests for syphilis are attempted

Late syphilitic lesions of the tongue are rare These may be isolated

gummas of the muscle but more usually are diffuse infiltrative lesions with less tendency to ulcerate than gummas in other locations

Leukoplakia of the oral mucous membranes occurs in sharply delineated greyish or silvery patches especially on the lateral borders of the tongue and at the angle of the lips In the former location it is deeply grafted into the mucosa and often the result of chronic irritation from tobacco or jagged teeth At the angle of the lips and just within the oral cavity, the lesion is superficial and widespread The consensus of opinion is that with leukoplakia on the buccal surfaces, syphilis is rare on the tongue, common Leukoplakia is of especial importance because it is presumed to be a precancerous lesion and as such should be treated promptly

Late Mucosal Syphilids of the Genitalia —Gumma of the penis is not uncommon and must be differentiated from chancroid, granuloma inguinale chancre, tuberculosis and carcinoma The lesion may cause great tissue destruction and deformity The regional lymph nodes are not involved Gummas of the external female genitalia, on the contrary, are exceedingly rare Practically all granulomatous lesions of the vulva formerly thought to be late manifestations of syphilis (esthiomene, elephantiasis vulvae), are due to lymphogranuloma venereum or to granuloma inguinale

Conditions Allied to Late Mucocutaneous Syphilis

Late Syphilis of the Nails —Syphilitic onychia occurs, when there is nodular infiltration of the nail bed but there are no distinctive characteristics whereby it can be differentiated from chronic onychia due to fungus infection, pyogenic bacteria, eczema or tuberculosis If there is an associated dactylitis of the terminal phalanx syphilis probably is the cause Lesions elsewhere, a positive serological reaction and improvement under antisyphilitic treatment establish the diagnosis

Late syphilis of the lymph nodes occurs as gummatous lymphadenitis, most often involving the cervical or inguinal nodes and is more common in negroes than in whites Periadenitis is common, and as the overlying skin becomes inflamed and adherent ulceration may supervene In the differential diagnosis tuberculosis and malignant lymphoma (Hodgkin s disease, lymphatic leukemia lymphosarcoma) must be considered Usually the lesion can be definitely identified only by a therapeutic test

Late Syphilis of the Bony Skeleton

Late syphilitic lesions of the bony skeleton[3] are not infrequent occurring in males slightly more often than females and in negroes nearly twice as frequently as in whites

During the early treponematemia organisms are carried into the deeper and more vascular layers of the periosteum also into the vascular sinuses of the marrow cavity and thence into the Haversian canals of the bony cortex The periosteal reaction begins as a diffuse or circumscribed subperiosteal infiltration in appearance like miliary gummas As contiguous layers of the cortex are involved osteoblastic activity is stimulated to form new bone and a proliferative hypertrophic lesion develops

In the medullary cavity late syphilis is essentially a gummatous process in the bony cortex a condensing osteitis Osteitis and osteomyelitis may be either predominantly proliferative or predominantly destructive the former more common than the latter in a proportion of about 10 to 1 at least in the long bones proliferation and destruction often are found together in the same lesion

Late osseous syphilis tends to involve the superficially located bones a fact which emphasizes the role of trauma in their evolution The nasopalatine bones most often are affected next the tibia skull and sternoclavicular region and with decreasing frequency the other bones The pelvic bones and the scapula well protected from traumatic insult are practically never involved

The most suggestive symptoms and signs of bone syphilis are pain and tumefaction The pain is deep seated aching and characteristically worse during repose i e usually nocturnal Tumefaction is readily apparent, if the involved bone is near the surface if deeply situated there may be palpated an ill defined thickening Tenderness on palpation is variable sometimes mild sometimes severe rarely as marked as in early periostitis In contrast to pyogenic infections fever and constitutional symptoms are conspicuously absent A characteristics feature of bone syphilis is that the symptoms are disproportionately less than *the roentgenogram indicates Indeed extensive lesions may be discovered* on routine roentgen examination despite the fact that no clinical symptoms or signs are present to signalize their existence

There is no evidence to suggest that systemic syphilis delays or alters the healing of fractures

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Juxta articular nodules are small densely fibrotic, gummatous nodules, usually symmetrically and subcutaneously situated about the extensor surfaces of the elbow or knee joints especially in women They are indolent and painless and may persist for years without softening or ulceration Similar lesions occur in acute rheumatic fever although in this condition they are more widely distributed and somewhat tender rheumatoid arthritis and in yaws Xanthomatous nodules are similar in appearance to the juxta articular nodules of syphilis If the lesions are due to syphilis, they disappear gradually when antisyphilitic treatment is instituted

Syphilis of the Circulatory System

Syphilitic Aortitis —By far the most frequent late visceral manifestation of syphilis in involvement of the ascending portion of the thoracic aorta Here the process is fundamentally a chronic mesaortitis with loss of elasticity and gradual dilatation under the stress of intra aortic pressure Pathologically the lesion consists of obliterative endarteritis of the vasa vasorum and infiltration of mononuclear cells into the media with gradual destruction of elastic tissue Intimal changes are secondary and appear typically as longitudinal wrinkling or irregular thickening occasionally with hyaline degeneration

The incidence of aortitis is placed by various writers as between 10 and 85 *per cent of all cases there being marked discrepancies between* its reported frequency as determined clinically and as demonstrated on post mortem examination These discrepancies result largely because of difficulties inherent in the clinical diagnosis of uncomplicated syphilitic aortitis

There is in the medical literature a controversy between those who consider uncomplicated aortitis an asymptomatic and undiagnosable condition[6] and those who believe its presence may be detected by means of appropriate clinical criteria[57] Resolution of their divergent opinions appears to depend largely upon definition of terms and recognition of the fact that syphilitic aortitis is always asymptomatic in its early stages giving rise to symptoms and signs as the weakened aorta (1) dilates (2) impinges upon contiguous structures (3) narrows the coronary orifices or (4) weakens the aortic ring, making incompetent the aortic valve

At first the involvement of the aortic wall may be so slight as to produce no symptoms and no physical signs Later there may be diffuse

Late Syphilis of the Joints

Late syphilitic arthritis, synovitis, is a not uncommon manifestation of late syphilis[3] The patient's complaint is of stiffness and arthralgia, usually in the larger joints, spine, knees hips ankles and shoulders There may be limitation of movement but usually no swelling, local heat or deformity and no constitutional reaction Roentgenograms are negative except when there is associated periostitis of the long bones near the involved joint The condition closely simulates subacute or chronic infectious arthritis and is differentiated from the latter only by the serological test and prompt response to antisyphilitic therapy

Hydrarthrosis is a rare complication of arthritis in late acquired syphilis, although it is observed not infrequently in associated with florid secondary syphilis or with late congenital syphilis It usually involves one or both knee joints and can be identified only by the positive serological test, association with other lesions of syphilis and by prompt response to specific treatment

Gummatous arthritis may occur in rare instances as the so called 'pseudotuberculous white swelling" This usually involves the knee, which becomes swollen, indurated and limited in motion Later there may be erosion of the joint capsule and skin with multiple sinus formation In contrast to tuberculous arthritis the articular surfaces seldom are destroyed, and ankylosis is rare

Syphilis of Muscles, Tendons, Bursas, Juxta-articular Nodules

Gumma of muscle may occur most commonly in the tongue sternocleidomastoidius or quadriceps femoris Lesions of other muscles most often are diffusely infiltrated gummas, which may ulcerate through the skin

Syphilitic tenosynovitis is rare, even when there is extensive involvement of attached muscles overlying skin or of the underlying bone

Syphilitic bursitis[31], first described by Verneuil most often is seen in the bursa over the patella or the olecranon process and usually is symmetric and indolent There may be merely an exudation of fluid into the bursa or a gummatous infiltration with subsequent ulceration or fibrosis The occurrence of indolent symmetric bursitis in a characteristic location without preceding trauma in the presence of a positive serological test for syphilis, suggests the diagnosis

So insidious and exquisitely gradual is the development of syphilitic aortitis that by the time the lesion is manifest the patients are of an age group in which hypertension and arteriosclerosis are common These conditions so closely mimic the symptoms and signs of aortitis that both must be excluded if the syphilitic nature of the process is to be indisputably established

Complications of Syphilitic Aortitis —Although the root of the aorta is the most frequent and earliest site of involvement in cardiovascular syphilis the process most often fails to extend downward sufficiently to involve the sinuses of Valsalva or the commissural attachments of the aortic valve That such extension occurs in some patients but not in others has been explained by Wilens[38] on the basis of variations in the amount of elastic tissue in the root of the aorta This author found the elastic tissue of the media to end more abruptly at the commisures in cases in which aortic insufficiency had failed to develop than in cases in which the valves were incompetent

Coronary Ostial Stenosis —Syphilitic mesaortitis may compromise the patency of the coronary orifices by extension downward or when the coronary vessels originate above the sinuses of Valsalva as a congenital anomaly Rarely does the process extend more than a few millimeters beyond the ostia of the coronary arteries The clinical picture is that of gradually diminishing cardiac reserve most often with anginal pain Complete coronary occlusion which occasionally eventuates is rarely compatible with life because of the size of the vessel involved although so slowly does the ostial stenosis develop that there may be opportunity for development of a collateral circulation via the Thebesian vessels The prognosis is grave In Pincoffs and Love s series[39] the average duration of life after the appearance of the first symptom was 4 3 months The pathological findings are those of acute or chronic myocardial ischemia

Aortic Insufficiency —Although syphilitic valvulitis has been described[40] its occurrence is rare Far more often the changes in the aortic valve leaflets depend on weakening of the adjacent wall about the aortic ring especially at the cusp s highest and lateral points of attachment although the cusps themselves may be secondarily and passively altered in much the same fashion as is the intima elsewhere

Aortic insufficiency develops in approximately 30 per cent of cases of syphilitic aortitis[41] Incompetence of the aortic valve with diastolic regurgitation of blood into the left ventricle at first produces no symptoms[42] Later, extensive changes occur in the heart and peripheral

aortic dilatation, fusiform aneurysm, which is detectable by appropriate roentgenological methods At this stage the diagnosis is suggested by such physical signs as paramanubrial dullness, tambour second aortic

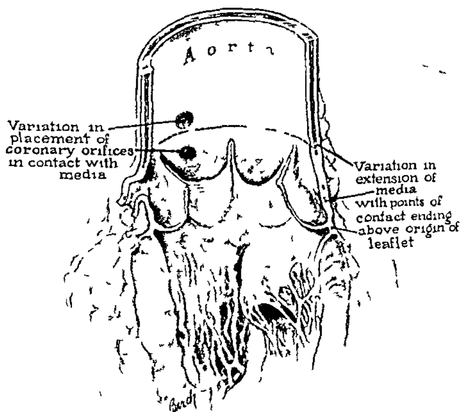


Fig Heart and aorta showing syphilitic aortitis

sound, systolic aortic murmur and increased pulse pressure The patient may complain of precordial pain aortalgia which characteristically is dull burning and relatively constant and of paroxysmal, asthmatoid dyspnea occurring without effort and most often at night

frequently is inequality of the radial pulses, anisocoria or a complete Horner's syndrome involvement of the recurrent laryngeal nerve and compression of the superior vena cava with impaired venous return from the head and arms. Aneurysms of the descending aorta may *impinge upon and erode the vertebra* Arising from any part of the thoracic aorta, the lesion may compress the lung (dyspnea) tracheobronchial tree (cough bronchostenosis) esophagus (dysphagia) pulmonary vessels (cor pulmonale) or other intrathoracic structures some especially those arising from the descending aorta, are completely *asymptomatic*

Many aortic aneurysms terminate in rupture into the pleural or pericardial cavity the tracheobronchial tree esophagus or externally following erosion through the sternum Death frequently is sudden from massive hemorrhage but may be preceded by intermittent oozing of arterial blood

Aneurysms of the *abdominal aorta*, especially those arising from its upper portion and those originating at the origin of the major upper branches (celiac and superior mesenteric arteries), usually are due to syphilis[44] Those lower in the abdominal aorta and of other branches are less often of syphilitic etiology instead they are more often arteriosclerotic (aorta) or mycotic (smaller branches) The most significant symptom is pain in the abdomen or back which characteristically is worse at night and relieved by change of position

Saccular dilatations involving the peripheral arteries also frequently are of syphilitic origin Almost any of the larger arteries may be attacked but particularly prone to involvement are the innominate and popliteal

Syphilitic Myocarditis —Invasion of the myocardium probably always occurs during the early treponematemia Several investigators have sought to demonstrate early involvement of the heart muscle by means of serial electrocardiograms but variables in the normal electrocardiogram and the non specific nature of the changes described cast doubt upon the significance of these studies Rarely a patient with early syphilis develops cardiac dilatation and myocardial failure which disappear after bed rest not to recur after antisyphilitic therapy has been administered

Gummas of the heart[45] are rare Either the pericardium or myocardium may be involved but most frequently the lesion is located at the base of the heart or in the intraventricular septum Disorders of the heart beat may be present if the conduction apparatus is involved

circulation Lowering of the diastolic pressure and compensatory systolic hypertension result in significant widening of the pulse pressure To maintain the integrity of the circulation and compensate for regurgitation, the left ventricle must eject a larger volume of blood at each systole In consequence of the increased work it is called upon to perform the ventricle dilates and becomes hypertrophied The heart also suffers, by virtue of a less efficient coronary circulation resulting from decreased diastolic pressure within the aorta Ultimately congestive failure ensues and once decompensation has occurred, remissions are rare Death usually is due to progressive heart failure, but often it is sudden and not infrequently inexplicable

The diagnosis of syphilitic aortic regurgitation presents few difficulties The symptoms are those of aortitis plus those referable to myocardial insufficiency, dyspnea, orthopnea, edema and chronic passive congestion of the viscera The signs are characteristic and easy to detect, cardiac enlargement to the left, forceful ventricular systole, the characteristic early diastolic blow, not infrequently associated with an aortic systolic murmur and/or the apical presystolic bruit of Flint and phenomena of the peripheral circulation which result from increased pulse pressure (collapsing pulse, capillary pulsations, etc)

Excluding arteriovenous aneurysm, which may produce the peripheral phenomena of widened pulse pressure, and dissecting aneurysm, which rarely mimics cardiovascular syphilis, the differential diagnosis necessitates exclusion of other causes of aortic valvular incompentency such as rheumatic heart disease hypertensive and arteriosclerotic cardiovascular disease and rupture of an aortic cusp

Aneurysm—When syphilitic aortitis occurs as a localized process, sacular dilatation may occur The out-pouching is a purely mechanical process, produced at a point of weakening by the hemostatic pressure within the vessel Hence aneurysms are more frequent in patients with hypertension and occur with decreasing frequency in vessels of decreasing caliber and intravascular pressure

Thoracic aneurysms are by far the most common The diagnosis is established by the demonstration of a mediastinal mass and proof, fluroscopic or roentgenkymographic of the vascular nature of this mass

The clinical manifestations[13] depend upon the location and size of the sacculation and the amount of pulsation within it Aneurysms of the sinus of Valsalva usually are small and not infrequently rupture into the pericardial sac Those of the ascending aorta may erode the sternum When the aortic arch is the site of localization there is not in

or endobronchial ulcerative or stenotic lesion There may be cough usually paroxysmal and productive dyspnea which may be either constant or paroxysmal and inspiratory stridor Atelectasis bronchiectasis and suppurative processes in the lung may occur distal to the site of obstruction The differential diagnosis includes bronchogenic carcinoma tuberculosis foreign body and bronchostenosis from extrinsic lesions such as enlarged lymph nodes or aneurysm

Pulmonary Syphilis—While *T pallidum* has never been incontrovertibly demonstrated in the lung of a patient with late syphilis there can be no doubt that late pulmonary syphilis exists[1]

Gummas may occur in any part of the lung These may in rare instances empty into a bronchus to produce a pulmonary cavity which as a rule heals with resultant fibrosis If sufficiently extensive pulmo lobatum results The coarseness of the fibrous bands the irregularity of their distribution and the lack of relationship to the bronchial subdivisions constitute strong presumptive evidence of syphilitic etiology Whether syphilis causes diffuse pulmonary fibrosis is problematical

Pulmonary syphilis gives no characteristic symptoms nor any distinctive physical signs and the roentgenological evidence is inconclusive Most often the clinical and pathological picture resembles chronic pulmonary tuberculosis The subjective complaints frequently are milder than the physical signs or the roentgenological changes would lead one to expect the patient's general condition ordinarily is good fever if present is of low grade The lower lung fields rather than the apices are more characteristically the sites of predilection for the gummatous process *Unresolved pneumonia formerly regarded as frequently* due to syphilis seems to be no more common among syphilitic than non syphilitic patients

Mediastinal Syphilis—Gummatous infiltration of the mediastinal lymph nodes is rare The symptoms are those of any mediastinal mass dyspnea cough dysphagia hoarseness edema of the head and neck with venous engorgement due to obstruction of the superior vena cava visible collateral circulation substernal discomfort and roentgenological evidence of a mediastinal tumefaction

Syphilis of the Digestive Tract

Esophagus—Involvement of the esophagus in the course of syphilitic *infection is a reportable rarity* The lesion whether localized gumma or diffuse gummatous infiltration may be primary in the esophagus or

There are reports of myocardial gummas becoming calcified or resulting in aneurysm of the heart

The myocardium is however, a relatively unfavorable site of localization for the organism of syphilis Few pathologists now concur in Warthin's conclusion that subclinical myocarditis occurs with great frequency in patients with late syphilis Love and Warner[16] have demonstrated that ischemic myocardial changes may occur as a result of coronary ostial stenosis associated with syphilitic aortitis Although never unequivocally proved by isolation of *T pallida* from the lesion itself, there is suggestive evidence that rarely true syphilitic myocarditis occurs[4] Certainly there are patients with syphilis, who develop unexplained myocardial insufficiency, and who either improve markedly following antisyphilitic therapy, or who are found to have post mortem evidence of chronic interstitial myocarditis of otherwise inexplicable etiology Saphir[18], who is not convinced that such cases are true syphilitic myocarditis, points out that the pathological changes are non specific and that merely because a patient has syphilis this does not prove the etiology of the myocardial lesion Until the incidence of myocarditis can be shown unequivocally to be higher among syphilitic patients than among non syphilitic persons, and until *T pallidum* can be isolated from the heart muscle of patients with otherwise unidentified myocardial lesions proof of the existence of late syphilitic myocarditis must remain sub judice

Syphilis of the Respiratory Tract

Laryngeal Syphilis —Late syphilis of the larynx[19] begins as a localized or more frequently, a diffuse gummatous infiltration, which may involve all or any part of the organ The resultant ulceration in healing, may cause laryngeal stenosis The most frequent symptom is hoarseness without pain Cicatricial changes may cause difficulty in breathing with stridor The differential diagnosis includes tuberculosis and neoplasm

Tracheobronchial Syphilis —Involvement of the tracheobronchial tree although rare is of considerable importance because it may if unrecognized, result fatally In Conner s experience[20] the lesions include (a) gummatous swellings either circumscribed or diffuse, (b) ulcers (c) endotracheal connective tissue new growth and (d) fibrous peritracheitis Ulcers occurred in 44 per cent of his cases being single or multiple often extensive and sometimes eroding the cartilages perforating the trachea or bronchi The symptoms are those of any endotracheal

A focal process in an organ with the functional reserve and capacity for regeneration as the liver seldom produces symptoms of hepatic insufficiency or of portal failure unless unusually extensive or so localized as to interfere mechanically with the circulation of blood or with the excretion of bile The most common clinical manifestations are abdominal pain weight loss indigestion and fever associated with a tender irregularly enlarged liver The therapeutic test may give the clue to the diagnosis

Spleen —Gummas of the spleen occur but present no characteristic clinical manifestations The diagnosis can be made only if there is rapid disappearance of a splenic tumor under antisyphilitic treatment Syphilis does not cause Banti s syndrome primary splenic anemia although hepatic syphilis may rarely be associated with splenomegaly and anemia thus simulating the syndrome

Pancreas —The only well authenticated cases of syphilis of the pancreas are *gummas which are sufficiently rare as to be pathological* curiosities Despite Warthin s claims diffuse interstitial fibrosis appears to be unrelated to syphilis Nor is there any relationship between syphilis and diabetes mellitus Joslin and his associates[8] were unable to find a single proved case of syphilitic diabetes in the literature nor in their own enormous material

Syphilis of the Genitourinary Tract

There is little evidence that syphilis is ever the cause of acute hemorrhagic nephritis There is even less proof that it is an etiological factor in nephrosclerosis In early acquired syphilis a nephrotic syndrome occurs with sufficient frequency and with such a dramatic response to antisyphilitic treatment as to preclude a chance association Moderate albuminuria which disappears promptly under treatment occurs in about 8 per cent of patients with secondary syphilis[9] Less frequently there is extensive proteinuria oliguria and minimal cylindruria associated with edema low plasma proteins and inversion of the albumin globulin ratio Significant elevation of the blood pressure retinitis impairment of renal function and hematuria usually are absent

In late syphilis there are two definitely identified specific lesions of the kidney neither of which ordinarily is apparent during life Gummas which are rare usually are small and of little clinical significance More *common are the focal lesions described by Rich*[60] *consisting of dense* accumulations of mononuclear cells in the interstitial tissues eventuating

extend from the mediastinum With healing there is cicatricial contraction and esophageal obstruction The differentiation of syphilis of the esophagus from carcinoma or achalasia of the cardia can be made only by esophagoscopy and biopsy, supplemented by fluoroscopic examination with barium and the therapeutic test

Stomach —Gastric symptoms are frequent in the course of syphilis, especially neurosyphilis, but rarely are they the result of involvement of the stomach itself

The histopathology of syphilis of the stomach [3] is essentially a granulomatous thickening and induration of the stomach wall, most marked in the submucosa Ulceration may occur Vascular lesions are described as a characteristic feature The entire stomach may be involved, with marked reduction in gastric volume the so called linitis plastica More frequently there is an annular localization, producing an "hour-glass" stomach In only one case of gastric syphilis has *T pallidum* been demonstrated by animal inoculation [4]

The clinical picture of gastric syphilis has been studied extensively by Lustermann and his associates , who emphasize the comparative youth of the patients, the marked and progressive nature of the gastric disturbances, the usual presence of achlorhydria or subacidity, and the usual absence of palpable mass, retention nausea, anorexia, anemia cachexia and gross hemorrhage The roentgenological manifestations usually are those of circumscribed or diffuse involvement of the stomach wall which produces contraction of variable degree, stiffening, lessened mobility and absence of peristalsis Gastroscopically [6] the normal gastric folds are effaced, and the mucosal surfaces appears granular Superficial ulcerations or localized or diffused infiltrative lesions may be identified

Intestinal Tract —Involvement of either the small or large intestine is among the rarest of syphilitic lesions Stricture of the rectum formerly thought usually to be due to syphilis, almost always is due rather, to lymphogranuloma venereum

Syphilis of the Liver, Spleen and Pancreas

Liver —Hahn [7] has demonstrated adequately that syphilis of the liver is primarily a focal gummatous process, which on healing results in large, irregular stellate scars, hepar lobatum There is good evidence that diffuse interstitial hepatitis cirrhosis occurs no more frequently in patients with syphilis than among non syphilitic persons The course of syphilis of the liver is benign

Inflammation of the iris occurs in two forms The more common type which occurs in the secondary stage or as a manifestation of early relapse differs neither in symptomatology nor in signs from iritis due to other causes There is a tendency to the formation of heavy posterior synechiae that may distort or even immobilize the pupil Secondary glaucoma is an infrequent complication The second type of syphilitic iritis is the so-called iritis papulosa a rare but characteristic lesion in which yellowish red nodules the size of a pinhead or larger are distributed over the surface of the iris

Syphilitic chorioretinitis probably has its onset in most instances early in the course of the disease although by the time the diagnosis is made the process usually is inactive and the syphilitic infection of many years duration The characteristic salt and pepper choroiditis of congenital syphilis is rarely if ever encountered in acquired syphilis Diffuse chorioretinitis affecting primarily the macula and posterior pole of the eye is not uncommon in acquired syphilis

Lesions of the optic nerve may occur either early or late The optic nerve may become inflamed in its intraocular portion optic neuritis or in its retrobulbar portion With acute or gummatous meningitis there may be choked disks that differ in no way from those caused by increased intracranial pressure due to other causes Primary optic atrophy commonly but not invariably associated with tabes dorsalis is the most grave of the ocular manifestations of syphilis The pathogenesis of this condition is unknown Its course is variable but the process almost always becomes bilateral If untreated it leads almost inevitably to complete bilateral blindness usually within a few years Only if the condition is recognized early and treated energetically with therapeutic malaria is the outlook good for preservation of vision

Several other ocular manifestations of syphilis should be mentioned Pupillary abnormalities such as inequalities in size irregularities in outline and sluggish to absent reactions to light are among the most frequent signs of neurosyphilis The Argyll Robertson pupil is essentially one that fails to react to light but does react on accommodation It is in addition one that is miotic and dilates poorly under mydriatics Paralysis of the motor nerves of the eye is commonly a manifestation of meningovascular neurosyphilis or of tabes dorsalis Gummas of the orbit and periostitis about the optic foramen occasionally are encountered

The Ear—Deafness due to syphilis occurs both in the acquired and congenital forms of the disease Auditory and more rarely vestibular symptoms may occur early as part of the syndrome of syphilitic menin

in more extensive cases in miliary focal cortical scars Amyloidosis occurring in late syphilis is similar in all respects to amyloidosis with other chronic infections

In early syphilis lesions of the *bladder* mucosa analogous to mucous patches elsewhere have been reported In late syphilis gummatous lesions of the bladder occur the cystoscopic appearance being that of nodular infiltration with or without ulceration The diagnosis can be made only by biopsy and a positive therapeutic test[61]

Paroxysmal Hemoglobinuria—The chief distinguishing characteristic of paroxysmal hemoglobinuria of the syphilitic type is the initiation of attacks by exposure to cold[6] The syndrome is to be differentiated from march hemoglobinuria, paroxysmal paralytic myoglobinuria and paroxysmal nocturnal hemoglobinuria, all of which are unrelated to syphilis

The relationship of cold hemoglobinuria to late usually congenital syphilis is well established by clinical and serological findings and by the response to antisyphilitic therapy Following exposure to cold there occurs a paroxysm characterized usually by a shaking chill, fever and the passage of urine darkened by the presence of hemoglobin Nearly all patients have some degree of anemia Vasomotor phenomena of the Raynaud type are not uncommon The serum of these patients contains a lysin having the peculiar characteristic of uniting with red blood cells only at low temperatures

Late Syphilitic Lesions of the Genitalia—In the female with the exception of chancre of the cervix, syphilis rarely involves the internal genital organs In the male well authenticated gummas of the prostate gland and seminal vesicles have been reported Warthin described interstitial fibrosis of the testis as a constant finding in late syphilis but the idea that such chronic fibrous orchitis is pathognomonic of syphilis is erroneous since similar changes occur with trauma infections and with advancing age Gummas of the testicle do occur and not infrequently soften break down and drain externally

Syphilis of the Eye and Ear

The Eye—Syphilis may involve almost any of the structures of the eye but its most important effects are seen chiefly in the cornea iris choroid retina and optic nerve[62] The cornea rarely is involved in acquired syphilis but interstitial keratitis is a common and characteristic affection of late congenital syphilis

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respond to those of the secondary stage of acquired syphilis Lesions of the skin and mucous membranes are characteristic The early cutaneous eruptions may be macular maculopapular vesicular (not seen in adults) or pustular Desquamation of the skin and moist papules between the gluteal folds are especially frequent Mucous patches may be found in the mouth or nose but are most common at the angles of the mouth Syphilitic rhinitis with snuffles is a common manifestation

Skeletal involvement is frequent the most characteristic lesions being osteochondritis osteoperiostitis and osteomyelitis Movements of the joints may be painful and at times the child has to be carried around on a pillow[5] In the most advanced cases pseudoparalysis results Visceral lesions are more constant and more extensive than in adults with the acquired disease and such conditions as diffuse hepatitis and pneumonia alba occur almost exclusively in infantile congenital syphilis The spleen usually is enlarged and the liver may be

Constitutional symptoms often are severe Anorexia and dehydration are frequent and the syphilitic infant seems to be unusually vulnerable to intercurrent infections of the respiratory and gastrointestinal tracts and to vitamin deficiencies

Latent Congenital Syphilis

As with the acquired form of the disease congenital syphilis may be latent from the start or pass into a stage of latency after the healing of early or late lesions The duration of the latent period is variable and late manifestations may develop at any time although rarely after the age of 25 years

Latent congenital syphilis differs from the latent phase of the acquired infection in the fact that there often are residual scars or malformations stigmas which although sometimes nonspecific constitute suggestive evidence of the disease These together with the results of serodiagnostic tests suffice to establish the diagnosis

Most of the stigmas of congenital syphilis are above the neck Of greatest diagnostic significance are

Facies The dish face resulting from a combination of frontal bossing saddle nose and prognathism together with a vacuous inalert facial expresion

Eyes Corneal scars from healed interstitial keratitis salt and pepper choroiditis

Nose Saddle nose the result of osteitis of the nasal bones

gitis or late, either in association with meningovascular neurosyphilis or as an isolated phenomenon Gummatous lesions of the cochlea and of the middle ear have been described[64]

Syphilis of the Central Nervous System—See description in Vol VI, pages 493, 559, 591, 617

Syphilis and Pregnancy

Syphilis is a less severe disease in women than in men The early manifestations of the disease tend to be less marked, and the grave late complications are significantly less frequent in females

Pregnancy exercises a beneficial effect upon the course of syphilitic infection When the disease is acquired simultaneously with, or subsequent to, conception, the early manifestations ordinarily are mild or absent altogether Moreover, women, who have had one or more pregnancies, are less likely to develop serious late manifestations than are those who are childless

Syphilis on the other hand, is deleterious to the outcome of pregnancy[6] The disease is a common cause of abortion, prematurity and still birth If the child is born alive, the probability of infection is high Whether the infant is infected, depends in part upon the duration of the maternal infection, it depends also upon the amount and nature of the treatment the mother receives prior to delivery

There is evidence that infection of the fetus rarely occurs until after the fifth month of pregnancy[66]

Congenital Syphilis

In general the clinical manifestations of congenital syphilis are comparable to those of the acquired disease The lesions of infantile congenital syphilis are similar to those of early syphilis in adults, latency occurs in the child as in the grown up and with a few important exceptions the late manifestations are not unlike those of the late stages of the acquired disease

Fetal infection often is overwhelming in nature as contrasted to the adult acquired disease The severity of congenital syphilis may be due to to route of inoculation, since in adults who are infected by the intravenous route as by blood transfusion the disease is characterized by widespread manifestations of unusual severity

Early Congenital Syphilis

In the more severe congenitally acquired infections evidences of the disease are manifest at birth or shortly thereafter These in general cor

considerable importance If the treatment has been adequate the child will escape infection if inadequate the manifestations of the disease in the offspring may be suppressed for varying lengths of time after birth

To establish or exclude the diagnosis of syphilis in such infants there are three procedures of practical value (1) clinical examination of the child (2) x ray examination of the long bones (3) repeated serological tests Dark field examination of scrapings from the umbilical vein if positive is definitive evidence of syphilis but rarely has this procedure been carried out when the infant was born Microscopic examination of the placenta and serological tests upon blood from the umbilical cord should be discarded as specific procedures

Physical Examination —In the absence of overt clinical manifestations of syphilis infection of the child is suggested by a failure to gain weight irritability restlessness the development of secondary anemia and the appearance of a nasal discharge Skin lesions if present may yield material for dark field examination

Roentgenologic Examination of the Long Bones —Syphilitic infection in infants frequently is manifested by involvement of the long bones (osteochondritis osteoperiostitis osteomyelitis) Roentgenologically the identification of these syphilitic bone lesions may be difficult Prematurely born non syphilitic babies frequently develop a symmetric periosteal reaction of the long bones that closely simulates early syphilitic osteoperiostitis Moreover the administration of bismuth to the mother during pregnancy results in the deposition of this heavy metal at the growing end of the long bones of the infant which is not unlike osteochondritis Osteomyelitis in infants may occur in the presence of such severe infections as meningococcus or gonococcus septicemia and streptobacillus infection X rays of the long bones of infants suspected of syphilis must be interpreted with caution The diagnosis should never be dependent upon this evidence alone

Blood Serological Tests —The blood serological tests of infants may be positive during the first few months of life because of passive transfer of maternal reagin through the placenta Usually within one month but invariably within three months this maternal reagin disappears spontaneously from the child s blood During this same period if infection is present but suppressed by inadequate treatment of the mother during pregnancy the child s blood test will become or remain positive usually in increasing titer

Whatever the variation of the serological tests during the first three months of life a confirmed positive test after that time is indicative of

Mouth "Rhagades", linear scars of periorificial infiltration with fissuring

Teeth (second dentition) —Peg shaped upper central incisors (Hutchinson), multifaceted "mulberry" first upper molars Dental hypoplasia notching wide spacing and malocclusion are common but occur also in other conditions

Palate Narrow highly arched palatal vault

Bony deformities "Saber shin" from periostitis of the tibia, 'scaphoid' scapula with a concave vertebral border

Late Congenital Syphilis

The overt late manifestations of congenital syphilis correspond in general to those of late acquired syphilis with certain notable exceptions Benign late lesions of the skin and bony skeleton occur Juvenile paresis[6] is the most frequent manifestation of congenital neurosyphilis Involvement of the cardiovascular system is remarkably unusual[68] and this fact constitutes the most striking difference between the congenital and the acquired disease

Four manifestations of late congenital syphilis, while not unique, are almost pathognomonic

Interstitial Keratitis —This is the most frequent ocular complication The mean age of onset is approximately 12 years although some cases occur before the age of 3 or after the age of 30 If untreated, the condition almost invariably involves both eyes

Nerve Deafness —Although perceptive deafness from involvement of the auditory nerve occurs in acquired syphilis (usually in association with acute syphilitic meningitis or meningovascular neurosyphilis) this condition is more frequent and more characteristic of the congenitally acquired disease

Symmetric Hydrarthrosis —Bilateral hydrarthrosis of the knee joints (Clutton's joints) is an infrequent but highly characteristic manifestation of late congenital syphilis

Paroxysmal cold hemoglobinuria is far more common in late congenital syphilis than in any other condition

Recognition of Syphilis in an Infant Born of a Syphilitic Mother

The diagnosis of syphilis in apparently normal infants born of mothers who have received antisyphilitic therapy, constitutes a problem of

considerable importance If the treatment has been adequate the child will escape infection if inadequate the manifestations of the disease in the offspring may be suppressed for varying lengths of time after birth

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congenital syphilis whereas a carefully checked negative test after three months means that the child has escaped infection

Third Generation Syphilis

Third generation syphilis[69], although rare, occurs in approximately 5 per cent of pregnancies in women with untreated congenital syphilis It is always the result of congenital infection in the mother and never of that in the father There is no evidence whatsoever that syphilis may be passed down through a family as a 'taint", nor that it ever occurs atavistically

Laboratory Tests in the Diagnosis of Syphilis

The development of the various laboratory aids has greatly facilitated the diagnosis of syphilis Laboratory tests do not and cannot replace clinical acumen, but they can and do complement a careful history and thorough physical examination

The definitive diagnosis of primary, secondary and latent syphilis depends largely upon laboratory confirmation In the tertiary stage the diagnosis not infrequently must be established on clinical grounds alone

Darkfield Microscopy

Treponema pallidum is demonstrably present in darkfield preparations only during the early stages of syphilitic infection It is quite useless to search for them in late lesions Specimens for darkfield study are readily obtained from accessible lesions on the skin and mucous membranes In the absence of lesions material may be aspirated from enlarged lymph nodes

Under the darkfield microscope *T pallidum* is identified by its morphological appearance, together with its characteristic types of movement Morphologically it is a delicate spirilliform organism with regularly spaced tightly wound coils which are constantly retained despite active motility The characteristic movements are three progression forward rapid rotation upon the long axis like a corkscrew and slow undulation The organism gives the impression of overall flexibility but most commonly flexion is near the middle It lacks the rapid lashing

movement of other spirochetes, many of which exist as saprophytes in the mouth or on the genitalia

T pallidum is the gentleman of the spirochete family, always maintaining his dignity of coil never thrashing aimlessly about he proceeds toward his destination with a certain savoir faire which allows time for a mannerly bow from the middle

Blood Serological Tests for Syphilis

There are at present only two types of blood serological procedures for the diagnosis of syphilis complement fixation and flocculation tests[9] Both depend upon the presence in syphilitic serum of a reacting substance called reagin Many variations of these two techniques are in use and the clinician frequently is more confused than assisted by the myriad of tests which are identified by the names of their respective original proponents

Although the blood serological test for syphilis is not specific in the sense of being a true antigen antibody reaction its value as an aid to diagnosis is well established When properly carried out and repeated so as to obviate technical error and secretarial mistakes in transcription of the report it may be regarded as highly specific for the disease

Biological false positive reactions must be excluded These in general are of low titer and frequently there are discrepancies between the results of flocculation and complement fixation tests Seldom do such tests remain positive more than 3 to 4 months There frequently is some clinical or laboratory evidence of the underlying condition responsible for the false positive reaction

A negative serological test does not exclude the possibility of syphilis Negative reactions are frequent in the first few weeks of the disease and they are not rare in late syphilis especially when the infection has been present for several decades Negative serological tests in overt secondary syphilis are however exceedingly rare

Serodiagnostic tests for syphilis may be quantitated the degree of positivity most often being expressed as the highest dilution of serum that gives a positive result The titer of the serological test has little diagnostic significance By and large the highest titers are observed in early syphilis in general paresis and in the presence of gummas but titers ranging from zero to several hundred may be encountered in any stage of the disease

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Serodiagnostic tests for syphilis may be quantitated the degree of positivity most often being expressed as the highest dilution of serum that gives a positive result The titer of the serological test has little diagnostic significance By and large the highest titers are observed in early syphilis in general paresis and in the presence of gummas but titers ranging from zero to several hundred may be encountered in any stage of the disease

Examination of the Cerebrospinal Fluid

In every patient with syphilis it is essential that the cerebrospinal fluid be examined at least once in a reliable laboratory, regardless of the results of the blood serological test Involvement, as opposed to invasion of the central nervous system almost invariably is detectable in advance of the development of clinical manifestations of neurosyphilis by study of the spinal fluid

The finding of cerebrospinal fluid abnormalities in a syphilitic patient in the absence of clinical evidences of involvement of the central nervous system makes possible the diagnosis of asymptomatic neurosyphilis The importance of this condition lies in the fact that since it precedes the development of clinical neurosyphilis its detection by means of routine spinal fluid study makes possible, by means of appropriate therapy, the prevention of development of the several syndromes of syphilis of the central nervous system

Routine examination of the cerebrospinal fluid should include a cell count, determination of the protein content and one of the colloidal tests These examinations although not specific for syphilis, give an indication of the activity of the syphilitic process in the central nervous system [1] The one test specifically indicative of neurosyphilis is the Wassermann reaction * which when quantitated, is a gross measure of the extent of the neuropathologic process

False positive cerebrospinal fluid Wassermann reactions are not unknown but occur only in the presence of conditions, such as meningitis, readily recognized clinically

Blood Cytology and Sedimentation Rate

During no stage of syphilitic infection are there striking changes in the blood cytology In early syphilis there may be mild leucocytosis and anemia Wile and his co-workers [2] have made these observations and describe also the occurrence of plasma cells and abnormal lymphocytes in the peripheral blood Microcytic anemia is not infrequent in patients with late syphilis especially those with chronic and incapacitating mani

* In the cerebrospinal fluid complement fixation tests are superior to any of the flocculation procedures because the spinal fluid unlike serum is almost completely free from a substance (probably contained in the albumin fraction) that tends to prevent the combination of antigen antibody and complement Although technically more difficult the complement fixation test is fundamentally the more satisfactory procedure

festations in infantile congenital syphilis this type of anemia may be severe. There is little evidence that syphilis per se results in microcytic anemia, although this has been reported in association with extensive osteosclerotic lesions and after gastrectomy for syphilis of the stomach.

The erythrocyte sedimentation rate is a non-specific reaction comparable to the body temperature and leucocyte count in that it gives information of a general character. In syphilis, as in certain other chronic infections, it is a gross measure of the extent and activity of the morbid process. The highest readings occur in association with florid secondary manifestations. In late syphilis erythrocyte sedimentation rarely is increased in the absence of overt clinical lesions.[4]

Neither the blood cytology nor the sedimentation rate has any diagnostic value in syphilis, except insofar as they may call attention to a more or less occult clinical condition. In following the course of syphilitic infection and assessing the response to antisyphilitic therapy, the quantitative serological test is a specific and far more reliable index of clinical activity.

PROGNOSIS IN SYPHILIS

Untreated syphilis does not invariably terminate in crippling or devastating manifestations of the disease. Bruusgaard's experience and other studies indicate that about 25 to 35 per cent of patients with untreated syphilis ultimately will achieve spontaneous "cure," and that an additional group of comparable size will remain free from all manifestations of the disease excepting positive reactions to serological tests. Thus well over half of those infected with syphilis live out their life expectancy without developing any serious evidence of syphilitic disease.

Others not so fortunate will suffer serious consequences. About 10 to 15 per cent develop benign lesions of the skin, skeleton or viscera which may be discomforting and deforming, but which in themselves do not cause death. Another group, some 10 to 15 per cent of the total, develops clinically manifest involvement of the central nervous system. A third group, comparable in size to the two preceding, suffers from lesions of the cardiovascular apparatus.

The extent to which syphilis shortens life expectancy has been estimated only on an overall basis, i.e., including in the study group persons with all types of infection ranging from primary syphilis to general paresis. On this basis various actuarial studies indicate that grossly life is shortened in syphilitic white males by about 17 per cent and in negro

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males by about 30 per cent [6] Unfortunately this is a statistically inaccurate and individually unjust approach to the problem So far careful actuarial studies are lacking of the risk to life, when patients are separated into groups by stage of infection, e g, early and late latent, cardiovascular, neurosyphilis, and still further separated by adequacy of modern treatment While it is certain that patients first recognized as syphilitic at a time when they have already developed grave late manifestations of the disease are poor actuarial hazards there are no data to indicate that those with adequately treated early or latent syphilis are worse life risks than non syphilitic persons of comparable age groups

Treatment of Syphilis

This is described in Chapter XXVIII-A which follows immediately after this chapter

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CHAPTER XXVIII A

SYPHILIS

PART II

THE TREATMENT AND PROPHYLAXIS OF SYPHILIS*

ARSENOBISMUTH MERCURY AND FEVER THERAPY

By JOSEPH EARLE MOORE AND HARRY EAGLE

PENICILLIN THERAPY

By HAROLD A TUCKER

The treatment and prophylaxis of syphilis is discussed under two subheadings Arsenobismuth Mercury and Fever Therapy and Penicillin Therapy the first by Moore and Eagle (see page 700) and second by Tucker (see page 706(151)) At the end of each of these subsections comes their Bibliography the first on page 706(125) the second on page 706(176) The discussion of arsenobismuth therapy as described in that *subsection has been continued* even though penicillin therapy described in the second subsection (see page 706(151)) very largely now has replaced it this has been done because in certain cases and perhaps in certain locations arsenobismuth therapy still is useful or must be employed for economic or other reasons and so the physician treating syphilis should have access to information as to its use Description of intensive arsenotherapy has not been included because no longer does it seem advisable because of the frequency of severe toxic reactions including a relatively high mortality rate following it and because penicillin can and should replace it Joseph Earle Moore

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ARSENOBISMUTH MERCURY AND FEVER THERAPY

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PENICILLIN THERAPY

PENICILLIN THERAPY

The Course of Syphilitic Infection as Modified by Treatment

The Course of Infection in Untreated Patients

The rational treatment of syphilis presupposes a thorough comprehension of the evolution of the disease the pathogenesis of its various complications and their prognosis Without that knowledge the physician must treat his patients by rule of thumb and can not evaluate properly the therapeutic response with that knowledge treatment becomes a flexible tool which may be adapted intelligently to the particular case Only the barest outlines of such a life history of syphilitic infection can be indicated here

The early manifestations of syphilitic infection are self limited Within 10 to 90 days after infection averaging 3 weeks there appears at the site of inoculation the characteristic lesion of primary syphilis the chancre At approximately the same time the regional lymph glands undergo a painless enlargement However long before this initial lesion has appeared syphilis has become a generalized systemic infection In experimental animals (rabbits) spirochetes have been demonstrated in the regional glands within 5 minutes[1] to 24 hours[2] after intratesticular inoculation and in the blood within one week Although the precise time relationships in man are not known a similar general dissemination undoubtedly occurs within a few hours or days The complete futility of the local treatment of a chancre is clearly apparent

The first outward evidence of the systemic nature of syphilitic infection is the development of the widespread and highly diversified secondary lesions Coming approximately 6 weeks after the original inoculation often while the primary lesion still is present usually these appear either as a generalized skin eruption or as lesions of the mucous membranes Like the primary lesion these contain the organisms in large numbers and tend to disappear spontaneously after a variable period Over the following 2 to 3 years there may be recurrent secondary lesions usually involving the skin mucous membranes eye or central nervous system Most patients then enter on a stage of latency of variable duration during which the only evidence of the disease may be a positive serological test

A certain proportion of rabbits inoculated with *T pallidum* are infected without developing a lesion at the site of inoculation[3] One can only speculate as to the frequency with which such symptomless infections occur in human beings Approximately 30 per cent of males and 60 per cent of females with syphilis can give no history of infection Even if we make allowances for the unobservant the mendacious and the

forgetful nevertheless it seems likely that symptomless infection is not uncommon

Once the patient has entered on the period of latency the course of late untreated syphilitic infection becomes variable in the extreme In some the disease remains latent and may disappear eventually leaving no trace In others there is a slow but progressive inflammation of invaded tissue with eventual fibrosis the degree of incapacitation depending on the tissue involved In yet others there may be a violent inflammatory reaction with marked tissue destruction despite the presence of comparatively few organisms

One factor which undoubtedly plays a part in the altered response of the patient with late syphilis to his infection is the development of a certain degree of immunity In both animals and man this immunity is reflected by a refractoriness to reinoculation The work of Chesney[4] indicates that this refractoriness is not necessarily contingent on the presence of syphilitic infection but persists after the complete eradication of the infection by antisyphilitic therapy so far as this can be determined In rabbit a variable but definite period must elapse after infection for this immunity to become manifest This may well be related to the fact that the rare cases of proved reinfection in human beings almost always occur in individuals who previously had had early syphilis treated and presumably cured before immunity could be established The nature of this immunity whether humoral cellular or a combination of both still is unknown and all attempts to immunize animals actively with the organisms and their products or passively with the serum of immune animals hitherto have failed

The factors which determine the course of infection and its localization are largely unknown The age race sex and constitutional background of the patient undoubtedly play an important part in influencing the degree and type of syphilitic involvement Thus in Table I* (after Turner[5]) the high incidence of bone and cardiovascular lesions in Negroes and the relatively low incidence of tabes and paresis is to be noted The generally fewer complications suffered by women is apparent also Indeed this is so marked as to suggest that pregnancy may in some manner serve to suppress the clinical complications of syphilitic infection

Differences in the virulence of strains of *T pallidum* and selective affinities of particular strains for certain tissues[6] have been reported in the experimental animal The relatively high incidence of neurosyphilis

Unless otherwise stated the tables in the following discussion are reproduced or modified from "The Modern Treatment of Syphilis" by J E Moore[6] Charles C Thomas Company Springfield Illinois 1932 (with permission of the publisher)

in the marital partners of tabetics and paretics[9] suggests that such organ affinities may play a part in human infection The evidence is, however inconclusive

With respect to the prognosis of untreated syphilis Reckzeh[10] estimates that one of every three syphilitics dies as a direct or indirect result of his infection Schroeder[11] shows that in an untreated or poorly treated

TABLE I

THE RACE AND SEX INCIDENCE OF VARIOUS SYPHILITIC LESIONS

(After Turner)

Type of lesion		Percentage frequency in			
		Whites		Negroes	
		Males 2 213 cases	Females 1 225 cases	Males 2 804 cases	Females 3 58 cases
Early syphilis involving**	Eye	3 5	1 9	9 5	4 8
	Skeletal system	0 4	0 6	3 1	1 7
	Nervous system	6 4	2 8	3 1	1 7
Late syphilis involving***	Skin and mucous membranes	7 8	11 6	9 0	8 3
	Bones and joints	6 0	5 8	12 6	8 6
Cardio vascular syphilis	Aneurysm	1 2	0 3	3 0	0 [illegible]
	Aortic insufficiency	2 8	1 4	5 0	1 5
	Aortitis other forms	4 7	3 1	9 9	5 0
Neuro-syphilis	Paresis	8 4	5 0	2 0	0 3
	Tabes	12 9	4 6	3 5	0 8
	All other	17 0	12 6	10 4	5 9
Latent syphilis		40 3	55 9	41 5	66 4

The incidence of some lesions in which there are no striking race or sex differences is omitted

In this group the percentages are expressed in terms of the total number of patients with early syphilis

In this and following groups the percentages are expressed in terms of the total number of patients with late syphilis

group the deaths were from 1 3 to 2 8 times greater than the expected mortality for the corresponding age groups the proportion varying with the duration of the infection More recent data[12] indicate that the life expectancy of syphilitics is 17 per cent less than that of a corresponding non syphilitic population

Perhaps the most important single study on the fate of untreated syphilis is that of Bruusgaard[13] based on the follow up in the years 1925

to 1927 of 2 181 cases of syphilis first seen in the years 1891 to 1910 and allowed to go without the treatment then current (mercury and potassium iodide). Of these 309 were available for re-examination and the cause of death could be determined in 164 others. The results are summarized in Table II.* As is there shown 22 per cent of the patients developed serious and often fatal late lesions, 12 per cent developed late lesions of the skin or mucous membrane, and in approximately 14 per cent the disease remained latent, the only evidence of the infection being the positive serological test. Finally, in no less than 14.1 per cent of the living patients the disease had "burned out" spontaneously, leaving no clinical or serological evidence of infection. Whether these were actually cured in the sense that the organisms had been eradicated completely is an open and perhaps academic question.

TABLE II

SUMMARY OF BRUUSGAARD'S DATA AS TO ULTIMATE OUTCOME OF UNTREATED EARLY SYPHILIS

Patients showing at re-examination or death	Per cent of total number (473 patients)
Neurosyphilis	9.5
Cardiovascular syphilis	12.8
Benign late syphilis	12
Latent syphilis (no clinical evidence, blood Wassermann positive)	14.1
Spontaneous "cure" (no clinical evidence, blood Wassermann negative)	7.9
Died of syphilis other than cardiovascular or central nervous system	0.8
Died of some other cause (cancer, tuberculosis, scattering)	2.6

The Evolution and Prognosis of Syphilis as Modified by Treatment

The extent to which the evolution of syphilis is modified by treatment and the prognosis of treated as against untreated syphilis depend on many factors, the most important of which are the duration and type of the infection and the adequacy of the treatment. These two factors are closely interrelated, and the necessity of adapting the treatment to the particular case will be stressed repeatedly throughout the following pages.

In bare outline in early syphilis adequate treatment may be defined

* The data are referable to the entire group only if we assume that the proportion of living and dead in the entire group do not differ significantly from those actually available for study.

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In late syphilis on the other hand actual biological cure probably is impossible and one must be content with symptomatic relief and the permanent arrest of the syphilitic process Serological reversal is not the goal of treatment nor does it parallel the symptomatic cure Where cardiovascular and neurosyphilitic involvement have been excluded as far as is possible by physical serological and x ray examinations the prognosis of late latent and benign skin and bone syphilis is in the main excellent and but few patients show clinical progression after adequate treatment even when the blood serology remains positive (Table III) In aortic insufficiency and aneurysm unlike simple aortitis permanent symptomatic cure is impossible Symptomatic relief can however be attained and life can be prolonged well beyond the 12 to 24 month life expectancy of the untreated patient

Half a loaf may be better than none and the patient with late syphilis is probably better off for having received even inadequate treatment In early syphilis on the other hand inadequate treatment may be definitely worse than none Not only does it predispose to infectious cutaneous and mucosal relapse (13 per cent as against 2 7 per cent in a group treated adequately) but also to such serious neurological relapses as neurorecurrence[14] and such ocular relapses as iritis uveitis and neuroretinitis[15] There is no satisfactory evidence that the inadequate treatment of early syphilis may predispose to late cardiovascular or neurosyphilis but it may definitely accelerate their development[16]

It seems entirely plausible that this paradoxical effect of inadequate treatment in early syphilis may be related to the fact that the patient has not as yet developed resistance to the organism or its products no matter whether that resistance rests on humoral factors or altered cellular reactivity Treatment by killing off most of the organisms halts that development and when treatment having been stopped prematurely the remaining organisms again begin to multiply they do not encounter the protective forces which the untreated patient would have elaborated in the meantime

This contrast between the ultimate fate of untreated inadequately treated and adequately treated cases of early syphilis is indicated clearly in Table IV

Methods of Evaluating the Drugs used in the Treatment of Syphilis

No compound should be suggested for the treatment of syphilis unless it has been studied carefully from several points of view

as a regime which includes at least 30 injections of an arsenical equivalent to arsphenamine and at least 40 injections of a heavy metal equivalent to bismuth within a period of at least 18 months No such definition even in approximation is feasible in the highly diversified late complications of the disease in which adequate treatment may vary between a relatively small amount of drug distributed over a period of years to an even more intensive regime than is recommended for early syphilis

The prognosis of syphilis treated adequately may be considered from three distinct points of view (1) biological cure which implies complete eradication of the infectious agent (2) symptomatic cure i e symptomatic relief and permanent freedom from further clinical progression and (3) serological cure i e the permanent reversal of the serological tests of blood and spinal fluid from positive to negative In all three respects the prognosis of early syphilis is more favorable than that of late syphilis and the more so the earlier treatment is instituted Indeed it is only in early syphilis that biological serological and symptomatic cure may all be attained The probability of such cure decreases from the 100 per cent of seronegative early syphilis to the 70 to 80 per cent of recurrent secondary syphilis (Table III)

TABLE III

THE PROBABILITY OF BIOLOGICAL SYMPTOMATIC AND SEROLOGICAL CURE IN VARIOUS TYPES OF EARLY AND LATE SYPHILIS

Type of syphilis		Probability expressed in approximate per cent if adequate treatment is given of —		
		Biological cure	Symptomatic cure	Serological cure
Early	Seronegative I	100	100	100
	Seropositive I	80–90	92–98	85–95
	Early II	80–95	92–98	85–95
	Recurrent II	70–80	70–80	70–80
Latent	Early	70–80	9[illegible]–98	80–90
	Late	0	90–95	30–35
Benign late	Skin or mucosa	0	90–95	30–40
	Bones and joints	0	80–90	10–25
	Other organs	0	60–80	30–40
Cardiovascular	Simple aortitis	0	70–80	30–40
	Aortic insufficiency	0	0	30–40
	Aneurysm	0	0	30–40
Central nervous system	Early	0	60–[illegible]0	85–95
	Diffuse late	0	40–60	30–40
	Tabes	0	20–35	60–70
	Paresis	0	15–30	0–10
Congenital	Early	40–60	40–60	40–60
	Late	0	0–80	10–20

peutic dose of any drug yet discovered. With the compounds hitherto available such curative doses would be dangerously close to the toxic range. It is necessary instead to use repeated doses, each only a fraction of the single curative dose in rabbits.

It follows that before a drug can be recommended for general use there must be an extensive clinical trial in large clinics under careful supervision. Such clinical trial includes (1) a study of toxic reactions both immediate and delayed, (2) the rate of disappearance of organisms from surface lesions, (3) the rate of healing, (4) the rapidity of serologic reversal under treatment, and (5) the ultimate clinical outcome.

ARSENICALS[20, 22]

The arsenicals regularly used in the treatment of syphilis are organic compounds in which the arsenic is attached directly to a carbon of the benzene ring. The prototype of the entire series is arsphenamine, the drug which revolutionized the treatment of syphilis after its discovery by Ehrlich in 1909. He called it salvarsan, and the name "606" refers to the fact that it was the 606th compound developed by Ehrlich and his coworkers in their search for an arsenical of value in the treatment of trypanosomiasis. All the compounds with trivalent arsenic now used are either derivatives of or closely related to arsphenamine (Table V). Although the formula for sulfarsphenamine given in Table V is the accepted one, recent work by Dyke and King[22a] strongly indicates that as ordinarily made sulfarsphenamine contains three methyl sulfonate groups, one attached to an amino and one to each hydroxy group.

Arsphenamine itself is sold as the dihydrochloride of 3-3 diamino 4-4 dihydroxy arsenobenzene. It is an amorphous yellow powder containing 30-31 per cent arsenic which dissolves slowly in water to form a strongly acid solution. This is highly toxic and *must be neutralized prior to use*. On the addition of alkali a gelatinous precipitate first forms, which is the free amino base; on the further addition of alkali this dissolves to form the monosodium salt. In actual practice a slight excess of alkali is added in order to form the disodium salt, which is said to be slightly less toxic[21]. Such alkalinized solutions are oxidized readily on exposure to air with a corresponding increase in toxicity[23] and solutions should not be used if more than 4 hours old.

Neoarsphenamine, the 914th compound in Ehrlich's series, is supposedly arsphenamine base in which one amino group has reacted with sodium formaldehyde sulfoxylate. Its arsenic content (19 per cent) is, however, even lower than its structural formula would indicate and implies the

(a) *Toxicity* — This includes not only the determination of the minimal lethal dose in experimental animals by various routes of administration but also the cumulative effect of repeated sub lethal and therapeutic doses supplemented by histopathological sections to detect sub clinical anatomical damage

(b) *Pharmacology* — Such preliminary studies must include also the rates of absorption and excretion by various routes of administration the tendency towards dangerous cumulative action pharmacological effects changes in blood chemistry and functional changes particularly of the liver and kidney

TABLE IV

An Estimate of the Probable Outcome in Early Syphilis Untreated Poorly Treated and Well Treated

Ultimate outcome	Probable outcome expressed in approximate per cent of		
	Untreated	Inadequately treated	Thoroughly treated
Serious late syphilis	25	35–40	5–10
Benign late syphilis	15	15	5
Latent syphilis	30	30	5
Cure	30	15–20	80–85

(c) *Treponemicidal Action in Vitro* — A pronounced treponemicidal action by a given compound on *T pallidum* in vitro may serve as a rough measure of its potential therapeutic activity The converse however is not necessarily true As evidenced by sulfarsphenamine[17] a compound may have little or no direct spirocheticidal action and yet be actively therapeutic by virtue of its conversion in vivo to other actively spirocheticidal agents The trypanocidal activity whether in vivo or in vitro has little or no necessary significance in relation to syphilitic infection[18]

(d) *Therapeutic Activity in Syphilitic Rabbits* — The amount of a given drug, administered in a single dose necessary to cure a syphilitic rabbit is a valuable index to its therapeutic activity The mere disappearance of organisms from an infected lesion does not suffice the lymph nodes must be removed from the infected rabbit and injected some weeks after treatment into a normal rabbit to establish cure [19]

(e) *Clinical* — The data obtained in animals although they supply a valuable orientation do not necessarily apply to human beings Not only may the rates of absorption and excretion differ but there may be toxic reactions not observed in the experimental animal Arsphenamine dermatitis and jaundice are cases in point Moreover unlike rabbits it is as yet not possible regularly to cure human beings with a single thera

admixture of a considerable amount of impurities Indeed none of the arsphenamines can be regarded as chemically pure compounds Dry powdered neoarsphenamine even in glass sealed ampules tends to deteriorate slowly on storage Harrison and Probey[24] recently have found that this deterioration may be retarded appreciably if the moisture content is kept below 1 5 per cent Neoarsphenamine readily dissolves in water or salt solution to form an approximately neutral clear yellow solution which may be injected without preliminary treatment It is even more susceptible to oxidation than alkalinized arsphenamine[25] with a corresponding increase in toxicity Solutions should therefore not be aerated and should be used immediately after preparation

Sulfarsphenamine has been generally considered to be an arsphenamine base in which both amino groups have reacted with sodium formaldehyde bisulfite and is so indicated in Table V It contains approximately 18 5 to 19 5 per cent arsenic is highly soluble and is far more stable with respect to oxidation than either arsphenamine or neoarsphenamine

Bismarsen a complex compound developed by Raiziss[8] apparently is a sulfarsphenamine like compound into which bismuth has been introduced although the tentative formula assigned to it has not been established Because of its high toxicity in intravenous injection it must be given intramuscularly

Silver arsphenamine developed by Kolle[7] is a complex arsphenamine containing approximately 12 per cent silver as AgO and approximately 19 per cent arsenic It dissolves freely in cold water to form a brown black solution and apparently is intermediate between neoarsphenamine and arsphenamine in its susceptibility to oxidation There is some question as to whether it is a definite chemical compound or a molecular mixture of neutral arsphenamine and colloidally dispersed silver oxide

'*Arsenoxide* (Mapharsen m amino p hydroxyphenyl arsenoxide) was a member of Ehrlich s series and was dismissed by him because of its high toxicity Recent reinvestigation of the compound by Tatum and Cooper[28] has revealed that it is also more active than the arsphenamines and that its chemotherapeutic index compares favorably with that of the arsphenamines Subsequent clinical studies[29] indicate that the drug in recommended dosage is at least as active as neoarsphenamine and almost never causes nitritoid reactions These early reports presage its use in an increasing rôle in lieu of the arsphenamines It is marketed in a glass sealed ampoule as the hydrochloride the ampoule containing inert substances and enough Na_2CO_3 to form an approximately neutral solution The powder is white to grayish white and forms a colorless solution which rapidly turns yellowish brown

TABLE V

THE ARSENICALS COMMONLY USED IN THE TREATMENT OF SYPHILIS

Acid Arsphenamine (the compound sold commercially) As = As HCl H_2N — NH_2 HCl OH OH Dihydrochloride of 3-3 diamino-4-4 dihydroxyarsenobenzene Molecular weight — 439 Theoretical As content — 31.2% Actual As Content — 31%	Arsphenamine (as injected after neutralization with 4 moles of NaOH) As = As H_2N — NH_2 NaO NaO Disodium salt of 3-3 diamino 4-4 dihydroxyarsenobenzene
Neoarsphenamine As = As H_2N — NHCH OSONa HO OH Sodium 3-3 diamino-4-4 dihydroxyarsenobenzene N methylenesulfinate Molecular weight — 466 Theoretical As content — 32.2% Actual As content — 20%	Sulfarsphenamine As = As NaO SOH_2CHN — $NHCH_2OSO_2Na$ OH OH Disodium 3-3 diamino 4-4 dihydroxyarsenobenzene N N dimethylenesulfonate Molecular weight — 598 Theoretical As content — 25.1% Actual As content — 19%
Mapharsen AsO NH_2 HCl OH Hydrochloride of 3 amino 4 hydroxyphenyl arsenoxide Molecular weight — 235.5 Theoretical As content — 31.8%	Stovarsol (acetarsone spirocide) AsO_3H_2 $NHCOCH_3$ OH 3 acetylamino-4 hydroxyphenylarsonic acid Molecular weight — 275 Theoretical As content — 27.3%

Tryparsamide AsO_3HNa $NHCH_2CONH_2$ Sodium salt of N phenylglycineamide p arsonic acid Molecular weight — 296 Theoretical As content — 25.3%

subcutaneously or intramuscularly presumably due to their slower absorption by the latter routes. These two compounds must be used intramuscularly. On the other hand neoarsphenamine is twice as toxic when given intramuscularly and both neoarsphenamine and arsphenamine are so irritating on local injection that they must be given intravenously. Autopsies of animals given lethal doses of these compounds shows[33] extensive tubular necrosis of the kidneys with deposition of calcium, focal necroses in the liver, spleen and myocardium, and a decrease in the lipoid and chromaffin content of the adrenal glands. With average therapeutic doses, however, tissue changes are minimal or absent.

Toxicity of Sublethal Doses. Pharmacological Effects. — When the arsphenamines are injected locally, they cause edema and local necrosis. As stated above, repeated intravenous injections in amounts comparable to those used therapeutically cause but inconspicuous tissue changes. Therapeutic doses in man usually have no effect on blood pressure, kidney function, coagulation time or blood picture. There may be a transitory albuminuria. Although liver function tests show evidence of slight liver damage in about 25 per cent of the patients, this rarely becomes of clinical significance.

The arsphenamines disappear from the blood soon after injection and only traces are demonstrable after 1 to 3 hours. With weekly injections there is definite storage. Although the lungs, kidneys and skin take up significant amounts of the arsenic after it leaves the blood, the largest part is retained by the liver. It is as yet unknown in what form the arsenic is stored or whether the stored compounds are treponemicidal. The arsenic is excreted largely in the urine and feces and is demonstrable in the urine within 1 hour and in the bile within a few minutes after injection. Fifty to 75 per cent is excreted within a week but there is a continued slow excretion for weeks thereafter. The chemical form of the excreted arsenic as yet is unknown.

Only negligible amounts of arsenic appear in the central nervous system[34] whether brain, spinal cord or spinal fluid after the intravenous injection of arsphenamine; moreover, the absolute amount of arsenic is not necessarily an indication of the therapeutic activity of the particular compounds which do finally get through, since an indeterminate proportion may be wholly inactive. The data of Table VII therefore do not necessarily or actually parallel clinical experience. Finally, although the measure of the trypanocidal activity of spinal fluid (Raiziss and Severac[34]) indicates that tryparsamide and sulfarsphenamine may be superior to other arsenicals in their ability to penetrate into the central nervous system, these results have no necessary validity with respect to

In addition to these trivalent arsenicals a pentavalent compound tryparsamide is widely used in the treatment of neurosyphilis This com pound N phenylglycineamide p arsonic acid synthesized by Jacobs and Heidelberger[30] is freely soluble as the sodium salt and forms a stable neutral solution

A second pentavalent compound stovarsol (acetarsone spirocide the sodium salt of 3 acetylamino 4 hydroxyphenylarsonic acid) developed by Fourneau[31] has been suggested for peroral use particularly in con genital syphilis[32] and will be discussed in that connection

Toxicity and Treponemicidal Activity

The toxicity of the various arsenicals may be defined in terms of (1) the minimal lethal dose or maximum tolerated dose on injection into experimental animals (2) pharmacological effects on administration of sub lethal doses in experimental animals and (3) toxic reactions observed in human beings which often find no counterpart in experimental animals (e g dermatitis jaundice optic atrophy caused by tryparsamide) This last group of reactions will be discussed in a following section

The Maximum Tolerated Dose —The maximum tolerated dose for the various types of arsenical is indicated in Table VI As there shown it is

TABLE VI

THE MAXIMUM TOLERATED DOSE OF THE VARIOUS ARSENICALS USED IN THE TREATMENT OF SYPHILIS

Drug	Maximum tolerated dose (mg/kg) in			
	Rabbits		Mice	
	Intravenous injection	Intramuscular injection	Intravenous injection	Intraperitoneal injection
Arsphenamine	75–150	150	100–400	00– 50
Neoarsphenamine	2?5–350	130–200	200–375	1 5 1/3
Silver arsphenamine	75–115	—	130–170	2 5–300
Sulfarsphenamine	275–400	500–,00	210–3 0	400–600
Bismarsen	36–40	300?	300	—
Mapharsen	1?–15	—	—	30–40
Tryparsamide	750–900	—	1000– 500	—

Unpublished data by Eagle numbers in this column represent amounts which will kill 50   of mice within 4 days

influenced significantly by the route of administration Thus sulfarsphen amine is almost twice and bismarsen is approximately ten times as toxic on intravenous administration as are these two drugs when injected

of the arsphenamine probably depends on its oxidation to arsenoxide. It is as yet an open question whether all the other arsphenamines are converted also to this specific arsenoxide, or whether the first step in the oxidative process, the conversion of the As=As to the AsO group without involving the other groups, alone suffices to produce an active compound.

The antispirochetal activity of the pentavalent arsenicals is too slight to explain their therapeutic activity, weak as it is. One must assume their conversion to other agents in vivo, perhaps to the corresponding trivalent arsenoxide.

The mechanism whereby arsenicals in general and arsenoxides in particular kill *T. pallidum* is still obscure. It has been suggested that their trypanocidal activity may rest on the fact that they combine with sulfhydryl group in the organism[4]. Certain it is that sulfhydryl compounds in sufficient excess inactivate both the trypanocidal[26] and the treponemicidal[27] activity of arsphenamines and arsenoxides. Although it does not follow necessarily that this affinity for sulfhydryl groups is the basis of their therapeutic activity, this theory constitutes a satisfactory working hypothesis.

Relative Therapeutic Activity of the Various Arsenicals and their Dosage[20]

The determination of the curative dose of a given drug in rabbits bears no necessary relationship to the therapeutic problem in man. Thus 15 mgm. per kilogram of arsphenamine may cure a rabbit. In a man weighing 150 pounds this corresponds to a dose of approximately 1 gram. Not only is this amount too toxic to use routinely as a therapeutic dose in man but clinical experience has shown that a single injection even in this amount does not suffice to cure human beings. The rabbit assay is nevertheless the best available criterion of treponemicidal activity short of clinical trial. In Table VIII are listed (a) the curative dose in syphilitic rabbits in mgm. per kgm., (b) the maximum tolerated dose in rabbits and (c) the resulting therapeutic index in rabbits for a series of compounds. In the same table are listed (d) the average therapeutic dose based on clinical experience and (e) the therapeutic index in man for each injection. The significance of the latter figure is impaired by the unjustified assumption that the toxicity in man and rabbit is of the same order of magnitude; the computation further ignores the possible cumulative effect of repeated injections. Nevertheless it probably represents the correct order of magnitude for the margin of safety in the therapeutic use of the arsenicals in man.

T pallidum or syphilitic infection The various methods which have been employed to increase the concentration of arsenic in the spinal fluid will be discussed in a later section

Treponemicidal Activity of the Arsphenamines — There is unfortunately at the present time no simple reliable test for the therapeutic activity of any antisyphilitic agent The measure of the trypanocidal activity whether in vitro or in infected rats although technically simple and reproducible is not necessarily a measure either of treponemicidal activity or of therapeutic activity in syphilitic human beings[18] Thus the pentavalent arsenicals generally are actively trypanocidal in vivo but have little treponemicidal effect The only experimental method of evaluating therapeutic potency now available is the treatment of rabbit syphilis, and this is so costly laborious and time consuming that it is not a practicable

TABLE VII

ARSENIC IN THE SPINAL FLUID (AFTER CORNWALL BUNKER AND MYERS[14] AND FORDYCE ROSEN AND MYERS[15])

Drug	Per cent of patients showing arsenic in cerebrospinal fluid	Average amount of arsenic present in mgm per 100 gm of cerebrospinal fluid
Arsphenamine	77 5	4
Neoarsphenamine	77	5–10
Silver arsphenamine	70–85	11 5–12 5
Tryparsamide	100	2–2 5

* This could not be confirmed by Vonkennel and Kimmig[3] who found no arsenic in the spinal fluid of 16 patients treated with tryparsamide

measure to apply to each manufactured lot of the various arsenicals The only control which is attempted is the control of toxicity administered by the U S Public Health Service at the National Institute of Health

Intimately related to the foregoing is the fact that as with most other chemotherapeutic agents the essential chemical mechanism whereby arsenicals kill *T pallidum* is largely obscure It seems clear that the arsphenamines as such either are not spirocheticidal or are only weakly so They are however so rapidly oxidized in solution to such highly active compounds that one may reasonably assume a similar oxidation in vivo to be the basis of their therapeutic activity[22] In the case of arsphenamine the first step in the oxidative process both in vivo and in vitro has been shown to be arsenoxide (m amino p hydroxyphenylarsenoxide) and this compound is so highly spirocheticidal[23] that the therapeutic activity

that of Cannon and Karelitz[40] who comparing arsphenamine and neoarsphenamine found arsphenamine to be definitely more active

(3) In evaluating the effect of treatment on the blood serological tests it is difficult to compare results obtained in different clinics because of the varying sensitivity of the tests employed Moore and Kemp[41] found that 80 per cent of their cases of early syphilis were rendered seronegative by 8 injections of 0 3 to 0 4 gm of arsphenamine alone This is to be compared with the 75 per cent reversal obtained by Harrison[42] with 10 injections of 0 6 gm of neoarsphenamine combined with simultaneous bismuth or mercury The validity of using the rate of serological reversal as a significant measure of activity has however been questioned by Moore and his associates[43] who found arsphenamine silver arsphenamine bismarsen and mapharsen in average therapeutic doses to be equally effective in causing serological reversal despite their known differences in therapeutic efficiency

Untoward Reactions Produced by the Use of the Arsenicals in the Treatment of Syphilis

Local Reactions — All the arsphenamines except sulfarsphenamine cause intense burning pain when injected into the tissues When in the course of an intravenous treatment some of the drug escapes into the surrounding tissues through faulty technic the injection should be discontinued immediately The degree of discomfort and its duration will vary according to the amount of drug which has escaped The arm merely may ache for a few hours there may be an exquisitely painful swelling lasting for days or even weeks with loss of function or if much drug has escaped the inflammation may result in necrosis and extensive anatomical damage

The best treatment is prophylactic i e to avoid tissue infiltration by careful technic and to discontinue injection at the first sign of extravasation or as soon as the patient complains of burning pain The intravenous injection of 10 per cent sodium thiosulfate into the same vein distal to the arsphenamine has been recommended to alleviate pain but in our experience this procedure is useless Later treatment consists of local hot compresses support of the arm and sedatives for the relief of pain

A correctly administered solution of over alkalinized arsphenamine may cause aching pain along the course of the vein and may result in thrombosis Not infrequently the veins may thrombose even if the arsphenamine is properly alkalinized and even if every precaution is taken to ensure an isotonic solution by dissolving the arsphenamine in

Relative Efficiency of the Arsenicals in Man

The evaluation of the therapeutic efficiency of any drug depends in the last analysis on the results obtained in man Four criteria are available three of which concern patients with early syphilis (1) the rate of disappearance of organisms from early lesions (2) the rapidity of healing of lesions and (3) the effect on the serum reagin titre in early syphilis (4) The fourth criterion the evaluation of the ultimate clinical outcome in various types of syphilis is clearly the one by which the worth of the drug must stand or fall Its definitive evaluation involves such close clinical observation over so long a time and in so large a group of patients

TABLE VIII

THE TREPONEMICIDAL AND THERAPEUTIC ACTIVITY AND THE CHEMOTHERAPEUTIC INDEX OF A SERIES OF ARSENICALS[39]

Drugs	(a) Curative dose in rabbits (mg/kg)	(b) Maximum tolerated dose in rabbits (mg/kg)	(c) Chemotherapeutic index in rabbits (approximate)	(d) Usual therapeutic dose in man weighing 60 kg (grams)	(e) Estimated chemotherapeutic index in man*
Arsphenamine	10–15	75–150	1 9	0 4	1 16
Neoarsphenamine	20–30	225–300	1 10	0 9	1 16
Silver arsphenamine	7–10	75–115	1 12	0 3	1 19
Sulfarsphenamine	12–17	200–300	1 15	0 6	1 25
Bismarsen	20	300 (I M)**	1 15	0 2 (I M)	1 30
Mapharsen	1 5–2 5	14–17	1 8	0 06	1 15
Tryparsamide	400	750–900	1 2	3 0	1 18

* Using data of column (b) for toxicity
** I M = intramuscular others are given intravenously

that only now are we beginning to obtain statistical results of significance These will be discussed in the following sections

(1) With respect to the immediate results in early syphilis[40] dosage is of paramount importance The larger the amount of drug used the more rapid will be the rate of disappearance of organisms and the healing of the lesions In general the effectiveness of the arsenicals in causing disappearance of organisms from surface lesions when used in ordinary therapeutic doses decreases in the order mapharsen arsphenamine silver arsphenamine sulfarsphenamine neoarsphenamine and bismarsen Tryparsamide is wholly ineffective in this respect and is of no value in the treatment of early syphilis

(2) One would probably place the arsenicals in the same order with respect to the healing of lesions The only careful study on this point i

nausea vomiting or diarrhœa coming on within 30 to 60 minutes after the injection and disappearing within a few hours The reaction can be prevented entirely if the tubing is soaked in 4 per cent NaOH for 6 to 12 hours before use and then is rinsed thoroughly

Smell and Taste Reaction — During the injection of arsphenamine or neoarsphenamine many patients complain that they can smell or taste the drug The odor is described variously as that of ether or garlic and is due to a volatile impurity which actually is smelled by the patient in that it becomes perceptible when the drug courses through the capillaries of the nasal mucosa If it proves very objectionable it may be prevented by having the patient breathe through his mouth during the injection holding his nose tightly with his fingers Alternatively the odor may be minimized by chewing gum or an after-dinner mint or by sniffing aromatic spirits of ammonia

Gastrointestinal Reactions — About 40 per cent of all injections of arsphenamine 25 per cent of neoarsphenamine and 15 to 20 per cent of silver arsphenamine are followed by gastrointestinal disturbances within 4 to 12 hours These last a few hours and are characterized by headache nausea vomiting and diarrhœa Mapharsen is said to cause such reactions less frequently (Gruhzit and others[29]) and they are also infrequent after bismarsen and sulfarsphenamine administered intramuscularly Dietary indiscretions such as a full meal just before or after the injection and constipation are predisposing factors The patient should be warned to eat lightly on the day of injection and to use a mild purgative if necessary on the day before treatment When these gastrointestinal upsets are repeated and prolonged a smaller dose or a shift either to another arsphenamine or to mapharsen may be beneficial

Angioneurotic Symptom Complex (Nitritoid Crisis) — The nitritoid crisis so named by Milian[45] because of its resemblance to the symptoms caused by amyl nitrite occurs in about one in every 200 to 1 000 injections particularly after neoarsphenamine and arsphenamine Early reports confirmed by our own experience indicate that it occurs only rarely with mapharsen[29] During or soon after the injection the patient complains of a feeling of heat palpitation and chest oppression Varying with the amount injected and the individual patient there may be cutaneous flushing cough vomiting back pain and a drop in blood pressure Rarely there is edema of the head region or even urticaria The symptoms last for 20 to 60 minutes and although the patient often has a sense of impending death a fatal outcome is almost unknown Prompt relief usually is obtained on the intramuscular injection of 0 6 c c of 1 1,000 adrenalin In very severe reactions with syncope and an almost

salt solution rather than water In such patients a shift from arsphenamine to some other arsenical is indicated Embolism from such thrombosed veins is uncommon, only one having been personally observed in many thousand instances of thrombosis

Solutions of mapharsen frequently cause exquisite pain along the course of the vein but very rarely thrombosis this may happen if the injection is prolonged unduly Unlike arsphenamine this compound must be injected in fairly concentrated solution and must be given rapidly

Systemic Reactions — Jarisch Herxheimer Reaction, Therapeutic Shock — Not infrequently the first injection of an arsphenamine is followed within a few hours by generalized aching and malaise fever and a temporary intensification of the manifestations of syphilitic infection Skin lesions may be intensified for several days, bone lesions may become painful Laryngeal gummata may become so swollen and edematous as to impede respiration and necessitate tracheotomy In cases of cardiovascular syphilis a Herxheimer reaction at the coronary orifices or in the wall of an aneurysm may prove fatal In cases of neurosyphilis with extensive vascular involvement cerebral hemorrhage is another danger

The cause of the reaction is supposed to be the sudden destruction of large numbers of organisms and the local release of their toxic products Where it may endanger the patient (not in early syphilis), it may be prevented either by prolonged preliminary treatment with bismuth (or mercury) and iodides or by beginning with relatively small doses of the arsenical (0 1 gm arsphenamine 0 15 gm neoarsphenamine 0 02 gm mapharsen) These preventive precautions are essential in laryngeal cardiovascular and visceral neurosyphilis and are employed by some in all patients with late syphilis on the theory that clinically undetectable vascular lesions may be present

Acid Arsphenamine — If arsphenamine is dissolved and injected without prior alkalinization death is almost inevitable if more than 0 gm have been injected and occurs within a few minutes Intravascular precipitation of the drug and the serum protein and agglutination of the red blood cells result in multiple minute pulmonary emboli A sense of oppression and pain in the chest and violent coughing are warning signals, which call for immediate cessation of the injection until the solution has been verified Adrenalin 1 to 1 000 0 5 to 1 0 c c intramuscularly or even intravenously in extreme emergency may be used to combat circulatory collapse If the patient survives the initial shock, absolute rest for two days is imperative

Tubing Reaction[11] — Certain brands of gum rubber tubing used in a gravity apparatus contain a toxic agent which may cause chills fever

TABLE IX

TYPES AND ESSENTIAL CHARACTERISTICS OF POST ARSPHENAMINE DERMATOSES

Type of eruption	*Special remarks*	Evidences of visceral associated damage	Expression of permanent sensitization	Further *arsphenamine* permissible
Urticarial	Part of angioneurotic reaction syndrome	0	0	Yes
Erythematous	Occurring early in treatment sometimes after first or second dose. Are symptoms accompanied by fever but no other constitutional symptoms of infection?	0	0	*Yes try* different product *in minute* dosage
Scarlatiniform			0	
Herpes simplex	Rare. Etiology unknown. Infection?	0	0	Yes
Herpes zoster	Rare. Etiology unknown. Infection?	0	0	Yes
Macular (morbilliform)	Beware of more arsphenamine if these eruptions are associated with marked itching or if the lesions tend to be scaly	*Unusual*	± to ++++	Doubtful use great caution
Maculopapular (erythematous squamous)				
Papulovesicular	Different degrees of the same phenomenon. Potentially serious	+ to ++++	++++	NO[1]
Vesicular				
Exfoliative				
Lichenoid	Probably a variety of the above	?	++++	NO[1]
Fixed exanthems	Not enough information available as to course under prolonged treatment	0	++++	Yes probably
Purpura	Associated with blood dyscrasias	++++	Not known but reactions prone to recur	NO[1]

[1] Especially renal damage, blood dyscrasias or hepatitis.

these two types of dermatitis cannot be made by the physician he should either consult immediately with an expert or temporarily withhold treatment until such consultation is available. If the lesions do not itch, blister, scale or exfoliate and further if they are not associated with constitutional symptoms or evidences of visceral damage, then when the lesions disappear spontaneously treatment may be re-instituted cautiously beginning with very small doses.

absent pulse 0 2 c c of 1 1 000 adrenalin solution may be injected intravenously *very slowly* Once the reaction has been observed in a given patient all subsequent injections should be given slowly and immediately discontinued on the appearance of conjunctival suffusion or flushing If the reaction persists adrenalin may be given intramuscularly 5 minutes before the arsenical If the use of adrenalin is contraindicated, as in hypertensive individuals in angina pectoris in severe cases of cardiovascular syphilis or by the symptoms it causes silver arsphenamine or mapharsen may be tried instead of arsphenamine and neoarsphenamine. Often the latter may be reintroduced with no difficulty after a lapse of several months

The cause of the syndrome is not entirely clear Rapid administration undoubtedly is the most important factor[46] yet in some patients it is observed despite painstakingly slow injection It rarely follows the first injection and some drugs tryparsamide and perhaps mapharsen rarely if ever cause it The similarity of the symptom complex to that caused by acid arsphenamine suggests a similar causation in keeping with this possibility Oliver and Yamada[47] have found that arsphenamines cause intravascular agglutination

Medical Shock Reactions[48] — In the rare patient the injection of arsphenamine may be followed immediately or after several hours by a condition resembling acute surgical shock characterized by pallor cyanosis nausea vomiting and collapse with weak pulse and low blood pressure It is not relieved by adrenalin but is combated by the application of external heat and the intravenous injection of 2 to 3 litres of sterile salt solution or 10 per cent glucose The possible role of adrenal damage in the causation of this syndrome is to be considered

Ventricular Fibrillation — The acute myocardial failure and death occasionally observed in patients with cardiovascular syphilis after the injection of an arsphenamine is assumed to be due to ventricular fibrillation and may be prevented by the proper therapeutic regime

Dermatitis[49] — A patient with syphilis is as susceptible to intercurrent infections and non specific dermatitis as is the non syphilitic person The antisyphilitic treatment may in addition lead directly to two types of skin involvement which differ enormously in their pathogenesis and prognosis One group consists of the relatively benign conditions listed in the first half of Table IX in which the unjustified withdrawal of the drug may expose the patient to the danger of untreated syphilis The others are among the most serious disasters of arsphenamine treatment are dangerous to life and definitely and permanently contraindicate further use of the arsphenamines When the differential diagnosis between

are of importance as predisposing factors It has been suggested[50] that the incidence may be reduced materially by beginning the treatment of late syphilis with a heavy metal rather than an arsenical This is as yet unconfirmed The successful sensitization of experimental animals to arsphenamine by Landsteiner and his coworkers[51] lends support to the thesis usually accepted that arsphenamine dermatitis is a manifestation of drug sensitization[52]

From the clinical standpoint the hypothesis of sensitization is strengthened by the fact that once a patient has developed dermatitis excessively minute quantities of the offending arsphenamine may suffice to precipitate a second attack Patients who develop dermatitis with any one of the arsphenamines usually are forever sensitive to all arsphenamines but not to inorganic pentavalent organic or even necessarily to other trivalent organic arsenicals Thus Jordan and Traenkle[29] found that three cases who had had arsphenamine dermatitis tolerated mapharsen well In our own experience however patients who have developed a sensitization dermatitis after an arsphenamine usually will reproduce the same reaction after mapharsen and the latter drug should be used with great caution in such cases In rare instances the patient is sensitive only to the one arsphenamine

The demonstration of hypersensitiveness by intradermal or patch testing[53] has failed to prove its usefulness[54] Occasional normals give positive results and many patients known to be sensitive give negative results

In case of doubt whether a given post arsphenamine dermatitis was due to sensitization one may begin cautiously the administration of minute amounts of some arsphenamine[55] as indicated in Table X only gradually increasing the dose and discontinuing treatment at the first sign of itching dermatitis fever or malaise Leucopenia eosinophilia or an increase in monocytes are danger signals Any patient known to be sensitive to the arsphenamines should be apprised of that fact and such treatment permanently interdicted to prevent another dermatitis and possible death at the hands of another physician

Argyria — The prolonged administration more than 20 to 25 injections of silver arsphenamine especially if associated with the administration of bismuth compounds may cause a dirty grayish blue discoloration of the skin and an intense pigmentation of the gums and buccal mucosa[56] This is permanent

Peripheral Neuritis — This is a rare treatment complication observed in less than 0 1 per cent of patients and usually only after a considerable amount of treatment The initial sensory symptoms numbness tingling

No attempt will be made to describe in detail the manifold appearances of the major arsenical dermatitides Usually they appear early in treatment commonly within the first twelve doses and at a variable period after the last injection There may be a prodromal period of several weeks duration during which malaise, fever and generalized itching follow each weekly injection in a patient who has such symptoms treatment should be suspended pending a careful checkup Usually the eruption begins on the extremities especially involving the flexor folds as at the elbows as a maculopapular or vesicular rash which spreads rapidly until the entire body is involved The skin may be thickened and in the severe cases marked scaling and exfoliation may occur lasting 3 to 4 weeks Itching often is intolerable The mucous membranes of the mouth conjunctiva vagina gastrointestinal tract and bronchi, may be involved also

Systemic manifestations may include, in addition to fever and prostration, kidney damage and extensive injury to the bone marrow, evidenced by leucopenia and eosinophilia Death occurs in about 10 per cent of the more severe cases usually because of some intercurrent infection occasionally because of anemia or of the lowered resistance to infection produced by the sequelæ of the liver or bone marrow damage

Nothing is known which significantly modifies the course or improves the prognosis of the complication Infection of the skin should be minimized by keeping the patient in sterile bed clothes with sterile bandages on the hands to prevent scratching Although the daily intravenous injection of 1 to 2 grams of sodium thiosulphate has been recommended highly, the experimental evidence and clinical results in different laboratories and clinics are so conflicting as to lead one to doubt that it has any value The daily intravenous injection of 1 gm of calcium gluconate 10 c c of a 10 per cent solution rests on almost equally shaky grounds and its value is equally dubious Intravenous injections of 5 per cent glucose are said to be beneficial

The cause of the vesicular and exfoliative types of arsphenamine dermatitis is thought definitely to be due to a sensitization phenomenon Its incidence after the administration of sulfarsphenamine arsphenamine neoarsphenamine and silver arsphenamine decreases in the order named It is as yet too soon to evaluate its incidence in patients receiving mapharsen In the case of arsphenamine and neoarsphenamine it occurs once in approximately every 150 patients is far more common with sulfarsphenamine and less common with silver arsphenamine Neither antecedent kidney damage the size of the dose the technic of administration age race or sex of the patient or the type of syphilitic involvement

treatment Three general types of dyscrasia are observed thrombocytopenia granulocytopenia aplastic anemia which may occur in combination Once a severe blood dyscrasia has been caused by an arsphenamine these drugs can never be used again and subsequent treatment is limited to the heavy metals Attempts to resume arsphenamine treatment always cause a recurrent reaction which may prove fatal Recently however mapharsen has been administered successfully without reaction to patients developing thrombocytopenia after the arsphenamines

In cases of thrombocytopenia the platelet count may fall to 50 000 within a few hours after the injection associated with the mucous and skin hemorrhages characteristic of purpura hemorrhagica There is no striking diminution in red blood cell or leucocyte counts and patients usually recover within 3 or 4 days It seems probable that the arsphenamines act directly on the circulating platelets as well as on the bone marrow

In granulocytopenia agranulocytic angina fever sore throat and soreness of the gums develop as long as 2 weeks after treatment There is a painful enlargement of the cervical glands which may extend to the adjacent soft tissues and there may be extensive necrosis of the pharynx and buccal mucosa Characteristically the white count is low in extreme cases as low as several hundred the decrease being largely in the granulocytes The disease is of several weeks duration and the prognosis is grave with the mortality in uncomplicated granulocytopenia approximately 33 per cent

In about half of the case not only the granulocytes but all the blood forming elements are affected with the clinical picture of aplastic anemia Apparently when the arsphenamines affect the bone marrow the platelets and granulocytic elements are the first to be involved and the erythropoietic elements are affected only by an intense intoxication Correspondingly the mortality in aplastic anemia is approximately 80 per cent There is progressively severe anemia involving platelets red cells and leucocyte with no evidence of regeneration

Striking results have been reported[6] in the treatment of agranulocytic angina by the injection of pentose nucleotide K 96 injected intravenously or intramuscularly in daily doses of 10 to 20 c c Clinical results may be apparent in 5 days In cases of aplastic anemia transfusion may be helpful as a temporary measure until bone marrow function is restored

Post Arsphenamine Jaundice — Jaundice is a common complication of arsphenamine therapy being observed in this country about once in every 75 patients and about once in every 1 000 injections Data from

of feet and hands tenderness of calf muscles may disappear if the drug is discontinued rarely there may be muscular weakness loss of reflexes wrist drop or foot drop atrophy and anesthesia Recovery in such cases is very slow

Hemorrhagic Encephalitis[57] —This uncommon complication usually develops after only a few injections Progressively severe headache develops 12 hours to a few days after the injection culminating in convulsions which recur at shorter and shorter intervals The temperature is very high and death usually occurs in 24 to 48 hours In mild cases the patient may recover after a few convulsions The characteristic pathological

TABLE X

SUGGESTED OUTLINE FOR TESTING FOR ARSPHENAMINE HYPERSENSITIVITY

1 Wait for all signs of original dermatitis to subside

Wait 2–3 more months

3 If original reaction was due to arsphenamine try neo or silver arsphenamine or mapharsen if due to neoarsphenamine try arsphenamine silver arsphenamine or mapharsen

4 Conduct experimental treatment as follows

Week	Dosage of arsphenamine or silver arsphenamine	Neoarsphenamine	Mapharsen
1	0 0 5 gms	0 025 gms	0 005 gms
2	0 05 gms	0 05 gms	0 010 gm
3	0 075 gms	0 1 gms	0 015 gms
4	0 1 gms	0 15 gms	0 020 gms
5	0 125 gms	0 2 gms	0 030 gms
6	0 15 gms	0 3 gms	0 040 gms
7	0 2 gms	0 45 gms	0 050 gms.
8 etc	0 3 gms	0 6 gms	0 060 gms

5 Stop permanently if itching dermatitis undue malaise fever or alterations in leucocytic blood picture occur

feature is cerebral edema with multiple minute hemorrhages Relatively large amounts of arsenic have been demonstrated in the brain[58] a finding which may be of etiological significance Schamberg and Wright[59] recommend the withdrawal of spinal fluid catharsis large doses of sodium bicarbonate and subcutaneous injections of 1 1 000 adrenalin

Transverse Myelitis —There have been a number of cases[60] in which the injection of an arsphenamine is followed several hours or days later by a paraplegia of spinal origin The prognosis for recovery is poor although a case may slowly clear up

Blood Dyscrasias[61] —The incidence of the blood dyscrasias fortunately is low with sulfarsphenamine the worst offender and neoarsphenamine next This complication usually is observed only after considerable

of several days with malaise fever nausea and epigastric distress there is a progressive jaundice of the obstructive type The liver is enlarged bile disappears from the stools appears in the urine and the bilirubin content of the blood serum is increased All liver function tests show evidences of impaired function which may persist for many months and according to Campbell and Soffer[9] even for years after clinical recovery The jaundice persists for an average of 10 to 14 days sometimes longer and then gradually fades

There is every possible transition between this mild type of arsphenamine jaundice and the severe and usually fatal course of acute yellow atrophy in which the liver rapidly shrinks In this extreme form there is intense jaundice fever vomiting drowsiness and coma with death in 7 to 14 days The ultimate fate of the mild cases still is in question O Leary and others have suggested that some eventually develop definite hepatic cirrhosis and as already stated persistent functional hepatic damage has been demonstrated years after clinical recovery In our experience however true cirrhosis has never been observed as a sequel

The treatment of post arsphenamine jaundice is symptomatic rest in bed with forced fluids saline catharsis a bland diet rich in carbohydrates and duodenal drainage with magnesium sulfate in cases of protracted jaundice The daily intravenous injection of 500 to 1 000 c c of 5 per cent glucose solution is of definite value and the daily intravenous use of 10 c c of 10 per cent calcium gluconate has been suggested also The chemical changes demonstrated in the blood of dogs with acute hepatic injury e g hemoconcentration hypochloremia[71] provide a rationale for treatment with intravenous injections of solutions of sodium chloride and glucose in addition to the measures just enumerated

Although antisyphilitic treatment with arsphenamine should be discontinued as soon as jaundice appears it may be resumed within 3 months after the jaundice has disappeared at first in minute doses (0 05 gm) gradually increasing until the average dose is reached There is almost never any complication In patients with early syphilis treatment with bismuth and potassium iodide should be continued during the course of the jaundice to avoid relap e especially neurorecurrence

Reactions Caused by Tryparsamide — Although tryparsamide very rarely causes either nitritoid crises dermatitis or jaundice it does have one grave complication visual damage[2] due to a direct toxic action on the optic nerve In about 10 per cent of the patients there is a subjective sensation of shimmering which comes on in 6 to 24 hours and which may be associated with dimness or veiling of vision There are few or no associated objective signs In an additional 5 per cent similar

England[63] and Germany suggest that arsphenamine is a more frequent offender than neoarsphenamine Reports in this country are conflicting[64] although the most recent exhaustive study of Soffer[65] also implicates arsphenamine more often than neoarsphenamine There are no valid statistical data as to silver arsphenamine and sulfarsphenamine

The etiology is still obscure Three theories have been suggested all of which have a certain amount of supporting evidence but cogent arguments can be raised against all three Against the hypothesis that the jaundice reflects direct liver intoxication by arsenic[66] are the following facts (1) arsphenamine jaundice rarely is associated with other forms of arsphenamine toxicity (2) jaundice appears anywhere from 1 day to 240 days after treatment while the excretion of arsenic is largely complete within a week and there is no evidence of its retention in the jaundiced individual (3) continued arsenical treatment of patients with arsphenamine jaundice has not affected them adversely and 4) the patient almost always can resume arsenical therapy with no ill effects on recovery from his jaundice

As an alternative theory[67] it has been suggested that the primary cause of the jaundice is not the arsphenamine but syphilitic involvement of the liver However the time of onset the pathological picture and the clinical course of the syndrome all seem inconsistent with that theory Only in a few instances does jaundice appear soon after treatment is instituted as a Herxheimer like reaction in a liver already involved by the syphilitic process

In two convincing statistical studies Ruge[68] has pointed out that in the German army during the years 1918 to 1929 there was a strikingly parallel increase in the incidence of post arsphenamine jaundice and the incidence of catarrhal jaundice in non syphilitic patients In view of the clinical similarity of the two conditions he has therefore suggested that so called arsphenamine jaundice is actually an epidemic disease occurring in a patient with syphilis This view is supported by Wile and Sams[68]

The severity of arsphenamine jaundice and the attendant symptoms may vary enormously About 25 per cent of all patients under arsenical treatment have an increased serum bilirubin significantly exceeding the normal level of 0 2 to 0 6 mgm per 100 c c but nevertheless under the 4 to 5 mgm which must be present before jaundice is clinically apparent[69] It is however debatable whether the clinical condition is merely an exaggerated form of this latent jaundice or whether they are entirely different in etiology and pathogenesis

The clinical picture of arsphenamine jaundice usually is indistinguishable from that of acute catarrhal jaundice After an indisposition

TABLE XI

BISMUTH PRODUCTS ACCEPTED BY THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION LISTED IN NEW AND NON OFFICIAL REMEDIES

Classification	Trade name	Chemical name vehicle of suspension or solution and concentration	Approximate percentage content of metallic bismuth	Recommended dose (intramuscular)†	Manufacturer or distributor
Insoluble suspended in aqueous medium	None				
Insoluble used in oil	Bismuth salicylate or subsalicylate	10 per cent suspension in peanut oil Each c c contains 0 13 gm of drug (Concentration varies with manufacturer)	64 0	0 2 gm (2 c c) weekly	Several manufacturers
	Oleobismuth	Bismuth oleate suspended in olive oil Each c c equivalent of 0 05 gm metallic bismuth	19 8	0 1 gm ([illegible] c c) once or twice weekly	Hoffman LaRoche Inc
	Tartroquiniobine	Suspension of quinine bismuth iodide 0 0[illegible]2 gm and sodium potassium bismuth tartrate 0 032 gm in 1 c c of oil	?	1–2 c c weekly	Spicer and Company
	Mesurol	Basic bismuth methoxy hydroxy benzoate 20 per cent suspension in sesame oil each c c equivalent of 0 11 gm metallic bismuth	54–57	0 [illegible] gm weekly	Winthrop Chemical Company
	Potassium bismuth tartrate	10 or 20 per cent suspension in almond oil with 0 6 per cent butyn	56 0	0 2 gm (2 c c) weekly	Abbott Laboratories

subjective complaints are associated with a concentric contraction of the visual fields particularly the nasal upper and lower portions Color sensation is unaffected Even when this constriction is severe it rarely proceeds to blindness provided only that the drug is discontinued The constriction of fields usually is observed before the fifth dose and if 1? doses are given with no impairment, the patient probably will not be affected subsequently by continued treatment

In a few patients and particularly if there is already some impairment of vision there may be a sudden loss of vision within 48 hours after treatment Although such patients may recover gradually the original level of visual activity is never attained

It follows that tryparsamide therapy should not be instituted unless the prospective gain exceeds the very real potential danger Its only proper use in syphilis is in the treatment of central nervous system syphilis Before treatment is begun the eyes should be examined the visual acuity noted and especially the visual fields recorded The patient should be warned to report visual disturbances and when they occur the eyes should be reexamined If there is any objective constriction of the visual fields treatment should be discontinued permanently If not treatment may be continued cautiously halving the dose and prolonging the interval between doses to two weeks

Bismuth

Bismuth compounds were introduced in the treatment of syphilis in 1921 by Severac and Levaditi[3] and since then largely have replaced mercury Well over 100 preparations have been marketed and the physician will find it difficult to choose among them In comparatively few have there been adequate pharmacological studies of toxicity absorption excretion et cetera Approval by the Council on Pharmacy and Chemistry of the American Medical Association implies that such laboratory studies have been made the compounds so approved are listed in Table XI

Mechanism of Action of Bismuth Compounds

Kolle[74] has pointed out that after bismuth is injected into syphilitic rabbits organisms disappear from surface lesions only after days or weeks instead of in hours as with the arsphenamines The curative dose nevertheless is surprisingly low[5] as low as 5 mgm per kgm with some of the alkaline tartrates This probably is to be ascribed to the fact that their

slow absorption and excretion makes for a low concentration in the tissues maintained for a long period of time

Levaditi and his coworkers[6] found bismuth compounds to have no treponemicidal activity but that on the addition of tissue extracts they became highly active both in vitro and in vivo They therefore postulated *the formation of a compound between tissue components and bismuth* which they termed bismoxyl Eagle[7] however recently has found all the water soluble bismuth compounds which he has studied to be actively spirocheticidal in the test tube and tissue extractives regularly have inhibited rather than increased that effect Moreover these compounds were active in such high dilution (in some experiments concentrations as little as 1 250 000 immobilized *T pallidum* within 2 to 4 hours) as to suggest that the slow killing observed in patients is due to a similar direct action on *T pallidum* As in the case of the arsphenamines the essential chemical reaction between bismuth compounds and the organisms responsible for the treponemicidal effect as yet is obscure The almost complete abolition of treponemicidal activity in vitro on the addition of sulfhydryl compounds (cysteine glutathione) in sufficient excess[37] may provide an experimental lead in this direction

TABLE XII

RELATIVE TOXICITY IN EXPERIMENTAL ANIMALS OF INTRAVENOUS AND INTRAMUSCULAR ADMINISTRATION OF SOLUBLE BISMUTH PRODUCTS

Drug	Lethal or tolerated single dose in mg/kg when given	
	Intravenously	Intramuscularly
Potassium bismuth tartrate	8–15	300
Bismuth sodium tartrate	15	250–600
Sodium potassium bismuth	30–50	200–800
Sodium iodobismuthite	30–60	1[illegible]0–130
Bismuth thioglycollate	18	24

Toxicity of Bismuth Compounds in Relation to Route of Administration

With the exception only of bismuth thioglycollate the soluble bismuth products now available are far more toxic on intravenous administration than they are on intramuscular injection This is shown clearly in Table XII As shown by Kolle[74] the therapeutic activity *of bismuth compounds* in syphilitic rabbits is however approximately the same by both routes The margin of safety accordingly is many times greater on

TABLE XI—Continued

Soluble used in oil	Bismo cymol	Basic bismuth campho carboxylate 0 05 gm in 1 c c	37–39	0 1 gm every 3–4 days	Abbott Laboratories
	Quiniobine	Quinine bismuth iodide rendered soluble in olive oil by means of lecithin Each c c contains 0 05 gm bismuth 0 03 gm quinine 0 075 gm iodine and 0 22 gm lecithin	?	1–2 c c twice weekly	Spicer and Company
	Biliposol	Alpha carboxethyl beta methyl nonoate of bismuth dissolved in olive oil each c c containing 0 04 gm metallic bismuth	45	2 0 c c twice to three times weekly	Ulmer Laboratories
Soluble used in aqueous medium	Bismosol	Potassium sodium bismuth tartrate in 10 per cent glucose solution 0 1 gm in 1 c c	41 0	0 1 gm (1 c c) twice weekly	Merck and Company
	Bismuth sodium tartrate	0 03 gm drug and 0 04 gm benzyl alcohol in 2 c c 50 per cent sucrose solution	73 8	0 03 gm 2–3 times weekly	G D Searle and Company
	Thio bismol	Bismuth thioglycollate 0 gm in 1 c c of distilled water	37 8	0 2 gm (1 c c) twice weekly	Parke Davis and Company
Soluble in ethylene glycol	Iodobismitol	Sodium iodobismuthite dissolved in ethylene glycol (0 057 to 0 066 gm per c c)	21 5	2 c c every 2–3 days	E R Squibb and Sons

* The approximate content of bismuth as noted is supplied in this column for the information of those interested It is as yet uncertain whether this has anything to do with therapeutic efficiency some investigators (Lomholt) holding that there is a rough parallelism between bismuth content and treponemicidal power others (Greenbaum) contending that there is no relationship Whatever the situation as to therapeutic efficiency may be there probably is some relationship between content of metallic bismuth and toxicity

† In this column dosage is expressed in terms of the drug mentioned It only adds to the general confusion to express it in terms of metallic bismuth Lomholt suggests however that adequate dosage is 0 5 mgm per kgm per week of metallic bismuth This implies of course that the bismuth content of the drug employed is definitely known

intramuscular injection and bismuth compounds should never be injected intravenously

Numerous attempts have been made to administer bismuth compounds orally bismutrat acid bismuth chloride[8] with liver extract water soluble potassium bismuth tartrate[?] and most recently sobisminol[80 81] have been recommended for that purpose The latter in particular has been studied extensively in experimental animals by Hanzlik Sollman and their respective coworkers and initial studies in human beings indicate a satisfactory degree of absorption The oral use of bismuth compounds is still however in the experimental stage and in the light of present knowledge the method should not be used in the treatment of patients

Absorption and Excretion in Relation to the Choice Between Water Soluble and Water Insoluble Compounds

Studies based on x rays of injected sites[8] chemical analyses of muscles in experimental animals at varying intervals after intramuscular injection[83] and chemical studies of bismuth excretion and storage[81], both in animals and man permit the following general conclusions

Approximately 70 per cent of the excreted bismuth appears in the urine and 30 per cent in the feces considerable amounts are stored in the tissues Evidence has been presented recently to indicate that the bones constitute a major storehouse[84] The rates of absorption and excretion of a series of bismuth compounds decreases in the order water soluble oil soluble and oil suspended Thus in the case of the water soluble thioglycollate 90 per cent is excreted in 2 to 3 days 10 to 20 days is required for the double tartrate while some of the oil suspended compounds are not completely absorbed after 100 to 200 days

Although a good deal of experimental work has been done on the tissue storage of bismuth compounds the clinical significance of these data is debatable The bismuth may be stored in an inactive form or it may be stored intracellularly where it cannot reach the organisms in the intercellular fluids The concentration of bismuth in the blood plasma probably is of greater significance with respect to the concentrations available in the tissue fluids It is apparent that water soluble compounds make for a relatively high blood level rapidly attained but of comparatively short duration With such compounds it is necessary to inject at fairly frequent intervals e g every two or three days as most of the bismuth is excreted within a few days On the other hand the insoluble compounds result in a far lower blood and tissue bismuth content than the peak concentration observed with the water soluble

compounds but this low level is maintained for weeks and months Unfortunately the information now available permits no choice on a priori theoretical grounds between these two schemes of treatment In favor of the water soluble compounds has been adduced the lessened danger of cumulative toxic effects and the absence of an accumulated reservoir should the patient develop toxic manifestations against them is the inconvenience discomfort and added expense of the more frequent injections they necessitate

Clinical experience with the several types of bismuth compound indicate that the suspension in oil type is at least as active therapeutically as either the water soluble or the oil soluble and there is no convincing evidence of a cumulative toxic effect Such suspensions accordingly are the compounds recommended for routine use with bismuth subsalicylate perhaps the drug of choice

Relative Efficacy of Bismuth and Arsenic Compounds

Bismuth cannot replace arsenicals in the treatment of syphilis It is far less effective a treponemicidal agent organisms disappearing from early skin or mucous lesions only after days rather than hours Its role is to supplement the arsenical holding the organisms in check in the intervals between the courses of arsphenamine It should be the sole drug used only when either the clinical condition of the patient e g cardiovascular syphilis or a serious toxic reaction to arsenicals e g dermatitis precludes their use Such data as are available indicate that bismuth is superior to mercury

Toxic Reactions to Bismuth Compounds

Experimental[35] — In animals given a single massive dose of bismuth compounds there is observed cloudy swelling of the liver with central necrosis marked tubular nephrosis and degenerative changes in the kidney resembling the effects of mercury poisoning Other organs are not affected markedly Repeated intramuscular injection in doses comparable to those used therapeutically has no demonstrable effect

Locally there may be necrosis of muscle fibres or small tender abscesses in the injected area In human beings however these local effects are not as pronounced

Clinical — Local Reactions — In general bismuth compounds injected intramuscularly are less toxic than mercurial compounds Among the insoluble compounds the tartrate is more painful than either the oleate

or salicylate and olive oil used as the suspending medium is more irritating than is peanut oil Sterile abscesses are rare In one clinic only five have been observed in a total of over 50 000 injections all five following the injection of the campho carboxylate Repeated aspiration with a 16 gauge needle or incision and drainage are indicated in such cases

Accidental Intravascular Injection — This may be prevented by using a large bore needle (19 gauge) and by aspirating for at least 5 to 10 seconds before the compound is injected to make sure a blood vessel has not been entered If an oil suspension of bismuth is accidentally injected intravenously there is the immediate effect of multiple pulmonary emboli with a subjective sensation of tightness in the chest and uncontrollable coughing Secondarily there may be the toxic and sometimes fatal manifestations resulting from the rapid absorption of bismuth from the multiple emboli If the injection is arterial the arterioles supplying that area of the buttock are plugged There is acute pain a mottled hemorrhagic eruption resembling cutis marmorata appears within 24 hours in the skin area supplied by the arterioles the buttock is indurated and there may be central necrosis and sloughing

General Reactions — *Bismuth Pigmentation in the Mouth* — After about six injections of bismuth most patients develop a bluish gray pigmented line at the margins of the gums resembling the lead line of lead poisoning As treatment continues this pigmentation may involve the buccal surfaces soft palate and inner surfaces of the cheeks This discoloration apparently is due to the deposition of bismuth perhaps as the sulfide in the summits of the oral papillæ It may persist for years but has no serious significance for the patient s health

Stomatitis — This occurs much less commonly after bismuth than it does after mercury As in mercury stomatitis secondary infection with the organisms of Vincent s angina is common The bismuth should be discontinued sodium perborate is applied locally as a wash and in case of Vincent s infection arsphenamine is injected intravenously Oral hygiene undoubtedly does much to minimize the incidence of stomatitis Severe bismuth stomatitis often is associated with a moderate to severe nephrosis (examine the urine!)

Effect of Bismuth on Kidneys — Although bismuth compounds in large doses produce extensive kidney degeneration in experimental animals no comparable lesions occur in the course of bismuth therapy in man except as above stated in association with severe stomatitis Kidney function remains normal and at most there is occasional albuminuria and cylindruria less frequent and less severe than after mercury

General Toxic Manifestations — Although liver damage with obstruc

tive jaundice various types of skin eruptions and secondary anemia have been reported after bismuth they are excessively rare and of little or no practical significance The association of bismuth with silver arsphenamine in the production of argyria has been described already

Herxheimer Effect — In keeping with the slow treponemicidal effect of bismuth compounds the Herxheimer effect i e the accentuation of syphilitic lesions after treatment is observed rarely and then only in the skin lesions of early syphilis Bismuth may therefore be administered safely in those conditions in which arsenical therapy would be dangerous e g gumma of the larynx certain forms of neurosyphilis cardiovascular syphilis

MERCURY[86]

Within one decade after the explosive appearance of syphilis in Western Europe in 149_ mercury was being widely used therapeutically It remained the drug of choice for 400 year until the advent of arsphenamine Thereafter it was used widely as an adjunct to arsphenamine but since 1921 it has been displaced gradually by bismuth There are as yet no thoroughly adequate statistical studies to show that bismuth is superior to mercury with respect to the ultimate clinical outcome the fact remains that the great majority of clinics have now discarded it in favor of bismuth compounds

Until recently there was no convincing evidence that mercury was of any value Recent studies however seem to show decisively that either arsphenamine and bismuth or arsphenamine and mercury used in conjunction are better than arsphenamine alone No logical explanation has yet been offered for the therapeutic effect of mercury compounds in syphilis Although strongly treponemicidal in vitro (dilutions of 1 50 000 may kill suspensions of *T pallidum* within 4 hours at 25 C) the single curative dose in experimental animals is practically the same as the minimal lethal dose Moreover the average therapeutic dose in human beings is so small a fraction of the curative dose in rabbits that any treponemicidal action it may exert must be excessively slow The suggestion that mercurials build up bodily resistance has no experimental basis and the term treponemistatic is satisfactory only because of its vagueness

Excretion[87]

After therapeutic administration most of the drug (60 to 75 per cent) is excreted by the kidneys a significant portion in the feces and traces in

the saliva and sweat Prolonged administration causes storage predominantly in the kidneys and liver In experimental animals large dose cause pathological changes[88] chiefly in the kidneys consisting of cloudy swelling fatty degeneration necrosis and calcification The convoluted tubules are involved particularly

Toxic Reactions in Man

According to Almkvist[89] the ulcerative stomatitis so often observed after mercurial therapy is caused by the deposition of mercuric sulfide in dental pockets where hydrogen sulfide is released by the action of putrefactive bacteria The resultant necrosis facilitates secondary invasion by Vincent s organisms The stomatitis is preceded by soreness of the gums aching of the teeth and salivation

Treatment of the stomatitis consists of mouth washes with either 2 per cent potassium chlorate or 1 4 000 potassium permanganate Arsphenamine applied locally will be of value in Vincent s angina The mercurial must of course be discontinued as long as the stomatitis persists

Gastrointestinal Disturbances — The oral administration of mercurials is not only relatively ineffective but is so likely to cause anorexia gastric distress nausea or diarrhea that it has been largely discontinued Some patients develop severe diarrhea no matter how the drug is given Treatment should be discontinued and the diarrhea treated symptomatically

Renal Damage — Average therapeutic doses may cause albuminuria and cylindruria or even a grave nephrosis Preexisting renal damage therefore contraindicates the use of the mercurials

Skin Eruptions[90] — These may be observed as a result of inunction Very rarely dermatoses may be caused by mercury no matter how administered

Seven Mercury Preparations and Their Administration

Seven different preparations representing three methods of administration their dosage advantages and disadvantages are summarized in Table XIII

Treatment by mouth is the least effectual method and should never be used in early syphilis Mercury protoiodide pills or so called mixed treatment (mercury bichloride 0 1 gm potassium iodide 16 gm with water to 120 c c) have been used for mouth treatment The soluble preparations suitable for intravenous or intramuscular use are particularly valuable in cases where the arsphenamines may cause a dangerou

TABLE XIII

THE ADVANTAGES AND DISADVANTAGES OF VARIOUS PREPARATIONS AND ROUTES OF ADMINISTRATION OF MERCURY

Route of administration		Preparation suggested for use	Dosage for adult	Advantages	Disadvantages	Indications for use
Inhalation		None	—	None	Dosage inexact, irritating to bronchial mucosa. Cabinet apparatus required	None
Mouth		Mercury protoiodide pill Mixed treatment	0.015–0.02 gm (1/4–1/3 gr) t.i.d. 4–8 c.c. t.i.d.	Easy to take. Inexpensive	Therapeutically inefficient. Poor absorption of pills unless freshly made. Prone to produce gastrointestinal disturbance	For very mild treatment in elderly or debilitated patients
Intravenous injection		Succinimide Cyanide Oxycyanide Benzoate	0.01 gm daily	Exact dosage, rapid absorption	Requires daily injection, expensive. Painful, sometimes thromboses vessel. Early toxic symptom	For rapid saturation with a heavy metal at start of treatment, especially in patients with cardio-vascular, visceral or neurosyphilis. A series should not exceed 20 injections
Intramuscular injection	Soluble salts	See above (intravenous)	0.01–0.02 gm daily or every other day		Painful, time consuming, expensive	See above (intravenous)
	Insoluble salts	None	—	Exact dosage, weekly treatment	Too dangerous, severe toxic symptoms frequent. If they occur, injected mercury cannot be removed	None. This method entirely replaced by bismuth
Inunction		25–50 per cent mercury ointment. The U S P is 50 per cent, may be diluted to 25 per cent with cold cream	4 gm daily. See special instructions in Table XIV	Therapeutically efficacious, inexpensive, painless, no danger of grave intoxication. *The best method of administration of mercury*	Valueless unless patient co-operates. Dirty, time consuming, may be revelatory of nature of disease. Therapeutic effect obtained only slowly, 4–6 weeks	Preferable to any other method unless very rapid therapeutic effect is desired when I V or I M injection of a soluble salt may be used

Herxheimer effect and where the action of insoluble bismuth compounds may be undesirably slow Their disadvantages are the necessity of almost daily visits to the physician and the high incidence of toxic complications

TABLE XIV

INSTRUCTIONS FOR THE PATIENT

The Rubbing Treatment

Read These Instructions Carefully

This is the best method of administering mercury but in order for the treatment to be successful *it is absolutely necessary* (1) *For you to understand* each step of the method and (2) for you to be willing to devote time and energy to it SUCCESS OR FAILURE DEPENDS ON YOU

Directions for Rubbing

The best time to rub is before going to bed *Take a hot bath beforehand* or if a complete bath is impossible wash well with soap and hot water the part to be rubbed that night

When thoroughly dry take out of the jar on the end of a spoon or spatula a *portion of ointment about the size of the end joint of your little finger* (as big as a large lima bean) Spread a little of this portion on the skin and with the *flat palm of the hand* rub it in slowly and not too hard putting on a little more ointment from time to time until the portion for that night has all been rubbed in This ought to take *20 minutes* and you should *time yourself* by a clock

Rub a different part of the skin every night of the week so that no part is rubbed more than once a week The rubbing should be done over a *part of your skin four times as large as your hand*

The best places to rub are —

First night — Upper part of one thigh in front
Second night — Upper part of one thigh in back
Third night — Inner sides of both arms
Fourth night — One side between hip and armpit
Fifth night — Other side between hip and armpit
Sixth night — Upper part of other thigh in front
Seventh night — Upper part of other thigh in back
Eighth night — Start all over again

Your back is a good place to rub if you have someone to do it for you *Avoid rubbing very hairy areas* such as the armpits *If pimples break out in any of these places* you are rubbing too hard

If after 20 minutes rubbing any ointment seems to be unabsorbed the excess may be wiped off the skin with a soft clean dry cloth or if preferred with a cloth soaked in a little benzene

While taking this treatment *please report in person or by letter* (1) two weeks after starting the treatment (2) once a month thereafter

Stop the treatment and report at once if

Your *teeth ache*
Your *gums become swollen* painful inflamed or bleed easily
You have *any persistent pain diarrhea* or *headache*

* At least one manufacturer puts up a weighed 4 gram dose of Unguentum Hydrarg in waxed paper This is the easiest method of prescribing the drug

The intramuscular injection of insoluble compounds is to be condemned, because of the excessive pain irregular absorption and cumulative toxic manifestations which cannot be avoided

The optimum method of administering mercurials is by the inunction of either the U S P preparation which contains 50 per cent mercury or of a somewhat diluted preparation should this prove irritating Directions for inunction which may be given the patient are shown in Table XIV It is economic for the patient and safe toxic manifestations are controlled immediately by the cessation of the inunctions At the same time it presupposes an intelligent and cooperative patient Moreover it should be borne in mind that although the inunction is therapeutically efficient it is a slow process 4 to 6 weeks of daily rubs are approximately as effective as a single dose of arsphenamine

The Iodides[91]

Iodides have little or no effect on the lesions of early syphilis There is however a general impression that they accelerate the healing of late lesions The mechanism of that effect is wholly obscure The iodides are not directly treponemicidal That they facilitate the penetration of the arsphenamines into relatively avascular lesions is a surmise for which there is as yet no experimental evidence The decreased antitryptic activity of the serum noted by Jobling and Petersen[9] after the administration of iodides may promote the proteolytic digestion of necrotic or granulomatous tissue Regardless of the mechanism of their action prolonged clinical observation has satisfied most syphilologists that the iodides do possess a healing power in late syphilis even though they may not cause either cure or arrest of the disease in terms of a direct effect on the organisms There are some however who maintain that the iodides add nothing to the effect of arsenical and bismuth compounds[93] The point is obviously almost impossible to settle based as it is on clinical impressions rather than objective measurements

Absorption and Excretion of the Iodides[94] — The iodides are absorbed rapidly no matter how administered and just as rapidly excreted No less than 96 per cent of iodides taken by mouth are absorbed and 25 per cent of iodides given by rectum The peak urine concentration is reached in 2 to 4 hours and 60 to 80 per cent is excreted in 24 hours almost all in the urine Although there is little or no tissue storage it is reported that a higher concentration is attained in syphilitic tissue than in uninvolved tissue

Therapeutic Administration — The complex and relatively expensive

organic compounds have no demonstrable superiority over sodium and potassium iodide which almost always are tolerated in high dosage with no disturbance For intravenous use the sodium salt must be used because of the toxicity of the potassium ion although somewhat more expensive it is said also to be absorbed more rapidly after oral administration

For general use except for the rare patient with a drug idiosyncrasy the drug is used in concentrated solution, 10 grams plus 10 grams water and may be taken in doses of 2 to 4 grams three times daily It is particularly indicated for use in conjunction with the appropriate arsphenamine or heavy metal in cases of late gummatous lesions in cardiovascular or hepatic syphilis acute syphilitic meningitis and for the relief of pain in bone syphilis

Contraindications and Toxic Manifestations —The iodides must not be used in cases of either tuberculosis or simple goitre In the former they may cause a redissemination of the infection in the latter they may produce or accentuate toxic hyperthyroidism many seem to doubt the latter possibility

The watery nasal discharge aching at the angles of the jaw and metallic taste often caused by the iodides ordinarily may be ignored Similarly the mild gastric irritation or iodide acne which some patients develop usually are not serious The rare patient may however have an extreme intolerance manifested either by edema of the head and neck so serious as to endanger respiration or by extensive and even fatal skin eruptions[95] Fortunately these phenomena are most uncommon

An occasional patient will have a mild febrile reaction several days after the ingestion of the iodides If this is repeated and is severe iodide therapy should be discontinued

Technical Aspects of Treatment[96]*

The Preparation and Administration of Arsphenamine

After the ampoule has been inspected and the label read a small but unmeasured quantity of sterile freshly distilled water is placed in a sterile Erlenmeyer or Florence flask with capacity 50 to 1 000 c c depending on the size of the dose to be prepared Approximately 5 to 10 c c of water is used per decigram of drug i e 20 to 40 c c for 0 3 to 0 4 gm 200 to 400 c c for 3 0 to 4 0 gm With the products of some manufacturers (see directions with the ampoule) hot water (160° F) facilitates solution and does not increase toxicity The neck of the ampoule is filed and

* The following outline of treatment technic is largely modified from Moore[4]

broken off and its contents are sprinkled or dusted not dumped on the surface of the water Arsphenamine is slowly soluble and tends to agglutinate into gelatinous clumps If allowed to stand 10 to 15 minutes are necessary for solution this may be hastened by sealing the flask with a sterile rubber stopper followed by vigorous shaking There is no danger of increased toxicity from shaking (aeration) of acid solutions of arsphenamine *Do not administer the acid solution it must be alkalinized or death may result*

After complete solution is obtained with no flaky or gelatinous particles still floating the drug is ready for alkalinization Alkalinization may be accomplished by the exact or by the approximate methods The United States Public Health Service and all manufacturers advise the former It is customary and advisable to use either normal 4 per cent or 15 per cent sodium hydroxide solution though for the approximate method a solution of unknown concentration may be employed

Exact Method — With a sterile pipette or burette 0 85 c c of 4 per cent or 0 227 c c of 15 per cent sodium hydroxide solution per decigram of drug is added all at once to the clear solution of acid arsphenamine Thus for 0 4 gm arsphenamine one uses 3 4 c c of 4 per cent or 0 9 c c of 15 per cent alkali These figures represent the correct amount of sodium hydroxide to form the disodium salt of arsphenamine This amount is approximately one third in excess of that amount which just suffices to redissolve the precipitate which first forms

Some workers feel that a mixture of the monosodium and disodium salts because it is less alkaline is much less likely to cause thrombophlebitis Such a solution may be prepared by adding only one fourth excess of alkali i e 0 64 c c of 4 per cent or 0 212 c c of 15 per cent alkali per decigram of drug

The Approximate (Drop) Method — While the exact method of alkalinization is used in most larger clinics the approximate method suffices in office practice Whether or not the concentration of the alkali solution is known it is added drop by drop until the yellow precipitate of arsphenamine base which first forms completely redissolves The drops should be counted Re solution of the precipitate should be facilitated by a swinging rotary motion of the flask but not by shaking since now aeration oxidation increases toxicity When the precipitate is completely redissolved one fourth excess of alkali is added i e if 12 drops were necessary to redissolve one adds 3 extra drops (The pH of a proper solution s about 10 and it is impossible to buffer it to neutrality without precipitation of the free base Moreover the alkaline solution is well tolerated if given slowly and well diluted Over alkalinization

organic compounds have no demonstrable superiority over sodium and potassium iodide which almost always are tolerated in high dosage with no disturbance For intravenous use the sodium salt must be used because of the toxicity of the potassium ion although somewhat more expensive it is said also to be absorbed more rapidly after oral administration

For general use except for the rare patient with a drug idiosyncrasy the drug is used in concentrated solution, 10 grams plus 10 grams water and may be taken in doses of 2 to 4 grams three times daily It is particularly indicated for use in conjunction with the appropriate arsphenamine or heavy metal in cases of late gummatous lesions in cardiovascular or hepatic syphilis acute syphilitic meningitis and for the relief of pain in bone syphilis

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* The following outline of treatment technic is largely modified from Moore[4]

The injection should be discontinued if the patient shows any signs of an immediate reaction It is highly desirable in sensitive patients to wait a minute or two after injection of the first 0 1 gm before proceeding with the rest of the injection When the necessary amount has been injected and the needle withdrawn sterile gauze is placed over the puncture and the patient instructed to keep it there for a few minutes If another injection is to be given and there is any suspicion of contamination of the tubing with blood the cylinder should be emptied and a new sterile tube used[6]

The Preparation and Administration of Neoarsphenamine

The administration of neoarsphenamine is much simpler than that of ars phenamine as it is readily soluble in a small quantity of water and need not be alkalinized There is no advantage to the gravity method with this drug and it is given usually by syringe injection

Only a single dose or at most no more than can be administered within 20 minutes is prepared at one time because of its rapid oxidation Ten to 15 c c of *cool* sterile freshly distilled water are placed in a small sterile beaker or medicine glass After the ampoule has been inspected and its label read its contents are sprinkled on the surface of the water The drug is readily soluble and will go into solution promptly with no agi tation whatever Shaking the solution or squirting it back and forth from a syringe increases toxicity and should be avoided The solution should be perfectly clear and transparent cloudy or flaky solutions must be dis carded The concentration of the solution is less important than with arsphenamine Although the United States Public Health Service advises a dilution of 10 c c per 0 1 gm drug much more concentrated solutions (as little as 2 to 4 c c per decigram) usually are employed Alkali must not be added and filtration also is unnecessary The solution should be injected immediately since it toxicity increases on standing Solutions more than 20 minutes old should not be used The only apparatus nec essary is a sterile all glass Luer syringe 20 to 30 c c capacity with stainless steel needles 20 to 24 gauge The injection must be given slowly to avoid immediate reactions Three to 6 minutes are none too long for a 0 6 to 0 9 gm dose

The Preparation and Administration of Silver Arsphenamine

This drug must be injected intravenously and either syringe or gravity methods may be used The directions given above for neoarsphenamine

causes pain along the vein during injection and subsequent thrombosis sometimes it may cause actual constriction of the vein wall rendering the immediate completion of the injection impossible)

The final dilution of the solution should be from 10 to 30 c c per decigram of drug i e 40 to 120 c c for a 0 4 gm dose The incidence of mild reactions is less with the more dilute solutions The final dilution may be with sterile water, or if desired with sterile normal salt solution The latter reduces the risk of thrombophlebitis Filtration of the solution through sterile filter paper cotton or gauze usually is advised

The properly alkalinized and diluted solution should stand for about 30 minutes before administration to permit completion of the chemical reactions Toxicity actually is reduced by this delay The solution may be allowed to stand for as long as three hours without increase in toxicity provided it is protected from the air is not shaken and the room temperature does not exceed 30° C (86° F)

A gravity apparatus (graduated cylinder rubber tubing* 4 to 6 feet long containing a glass window a few inches above the lower end a Mohr pinchcock for cutting off the flow Luer adapter stainless steel needles with slip joint 19 to 20 gauge) properly sterilized before use is preferable for administration In its absence a 50 c c syringe may be used though this is less desirable since (1) the rate of flow is harder to control (2) the solution of the average dose is too concentrated and (3) such large syringes are expensive and the breakage rate is high

The gravity apparatus should be arranged to provide a column of fluid not over 3 feet in height The tubing is rinsed with sterile water the cylinder and tubing are filled with solution and the air† expelled by lowering the end of the tube below the level of fluid in the cylinder

The patient should lie comfortably on his back on a couch or treatment table

The Rate of Injection — If the specifications as to the gauge of needle et cetera have been followed the correct rate of injection is practically insured by the size of the needle and the length of the tubing However this should be checked always In no case should the rate exceed 25 c c in one minute or a dose of 0 4 gm in four minutes five minutes is preferable The rate of flow should be even as well as slow

* *Caution* — Before being used the first time the tubing should be filled with 4 per cent sodium hydroxide solution for not less than 6 hours Then it should be rinsed thoroughly in water sterilized by boiling and thoroughly rinsed with sterile water again just before using This is necessary in order to prevent the tubing reaction

† The danger of air embolism is exaggerated as the accidental intravenous injection of 4 to 5 c c of air usually does no harm It should of course be avoided but physician and patient need not be unduly alarmed if it occurs

The injection should be discontinued if the patient shows any signs of an immediate reaction It is highly desirable in sensitive patients to wait a minute or two after injection of the first 0 1 gm before proceeding with the rest of the injection When the necessary amount has been injected and the needle withdrawn sterile gauze is placed over the puncture and the patient instructed to keep it there for a few minutes If another injection is to be given and there is any suspicion of contamination of the tubing with blood the cylinder should be emptied and a new sterile tube used[4]

The Preparation and Administration of Neoarsphenamine

The administration of neoarsphenamine is much simpler than that of arsphenamine as it is readily soluble in a small quantity of water and need not be alkalinized There is no advantage to the gravity method with this drug and it is given usually by syringe injection

Only a single dose or at most no more than can be administered within 20 minutes is prepared at one time because of its rapid oxidation Ten to 15 c c of *cool* sterile freshly distilled water are placed in a small sterile beaker or medicine glass After the ampoule has been inspected and its label read its contents are sprinkled on the surface of the water The drug is readily soluble and will go into solution promptly with no agitation whatever Shaking the solution or squirting it back and forth from a syringe increases toxicity and should be avoided The solution should be perfectly clear and transparent cloudy or flaky solutions must be discarded The concentration of the solution is less important than with arsphenamine Although the United States Public Health Service advises a dilution of 10 c.c per 0 1 gm drug much more concentrated solutions (as little as 2 to 4 c c per decigram) usually are employed Alkali must not be added and filtration also is unnecessary The solution should be injected immediately since its toxicity increases on standing Solutions more than 20 minutes old should not be used The only apparatus necessary is a sterile all glass Luer syringe 20 to 30 c c capacity with stainless steel needles 20 to 24 gauge The injection must be given slowly to avoid immediate reactions Three to 6 minutes are none too long for a 0 6 to 0 9 gm dose

The Preparation and Administration of Silver Arsphenamine

This drug must be injected intravenously and either syringe or gravity methods may be used The directions given above for neoarsphenamine

apply equally to silver arsphenamine As with neoarsphenamine the water used for solution must not be hot the solution must not be shaken or alkalinized and it must be used fresh The solution should be perfectly clear like black coffee and cloudy solutions or those containing insoluble matter should be discarded The concentration of the silver arsphenamine solution should be slightly less than with neoarsphenamine e g 25 to 30 c c of water for 0 3 gm drug Filtration is advised by the manufacturers but has proved to be unnecessary At least 3 minutes should be allowed for the injection

The Preparation and Administration of Sulfarsphenamine

This drug must be given intramuscularly it should never be used intravenously Highly concentrated solutions are better tolerated than dilute solutions An ampoule containing the proper dosage is inspected and the neck filed and broken One to 2 c c of *cool* sterile water (1 c c for doses of 0 3 gm or less 1 5 c c for 0 4 to 0 5 gm 2 c c for 0 6 to 0 8 gm) are added to the ampoule with a sterile 2 c c Luer or tuberculin syringe (preferably the latter) The drug is rapidly soluble The solution is aspirated into the syringe and injected intramuscularly

The Preparation and Administration of Bismarsen

This is identical with that of sulfarsphenamine The manufacturers supply a solvent containing 0 25 per cent butyn to minimize pain but sterile distilled water is equally satisfactory The drug may be mixed in the ampoule or in a sterile medicine glass 1 5 to 2 0 c c of water is adequate to dissolve the 0 2 gm dose Administration is intramuscular[6]

The Preparation and Administration of Mapharsen

Mapharsen is sold as the amine hydrochloride in a sealed ampoule which contains also just enough alkali to form a neutral solution on the addition of water The ampoule also contains some inert sucrose Unlike arsphenamine the contents of the single dose ampoule should be dissolved in a minimum amount of water (10 c c or less) and the solution should be thoroughly aerated by squirting back and forth in the syringe in order to remove the excess CO_2 Moreover and again in contrast to the arsphenamines the injection should be as rapid as possible as on slow injection patients often complain of severe and sometimes agonizing pain along the course of the vein Accordingly 1 to 1 5 c c of sterile water are added to

the ampoule A slight evolution of CO_2 is noted as the powder dissolves When solution is complete the contents of the ampoule are aspirated into a syringe containing approximately 9 c c additional water The contents of the syringe are shaken back and forth to insure complete admixture and then are injected intravenously through a 21 gauge needle

The Preparation and Administration of Tryparsamide

This drug is an easily soluble white powder The maximum dose of 3 0 gm may be dissolved in 10 to 20 c c of sterile freshly distilled water and administered by the syringe method Unlike the arsphenamines *toxicity is not increased by heat or aeration and shaking and squirting* to effect solution is permissible Moreover immediate shock like reactions do not occur and the speed of injection is unimportant

In rare instances when the patient has no veins suitable for in travenous injection tryparsamide may be given intramuscularly in con centrated solution (3 0 gm in 3 c c of water)[6]

General Considerations of Intra enous Technic

No elaborate precautions are necessary save for the sterility of the materials used The patient should be told to avoid food for a few hours before and after the injection

It is of course assumed that the physician is sufficiently expert in the technic of intravenous injection to assure the patient of a reasonably painless injection and to ensure also that the patient will not be exposed to the acute pain and subsequent discomfort caused by a mistaken in jection into the subcutaneous tissue

The needle should be of stainless steel medium bevel and with pointed tips 18 to 20 gauge for arsphenamine and 21 to 24 gauge for the other drugs and should be sharpened by an expert after every 12 to 15 punctures

Although other veins may be used if necessary the veins of choice are the median cephalic and median basilic just distal to the elbow Alcohol suffices to cleanse the skin iodine is not necessary nor need the skin be anesthetized The application of a tourniquet on the upper arm and a clenched fist make the veins stand out

The needle is inserted into the skin at an acute angle and is advanced about ½ cm before the vein wall is punctured It is essential that a free flow of blood be obtained before the injection is given the blood being allowed to flow either through the unattached needle through a 3 way

stopcock just behind the needle or if the needle is attached to a syringe directly into the barrel The tourniquet then is released and the injection begun The injection must be terminated at once if the patient complains of sharp burning pain at the site or if there is a visible subcutaneous bump This is caused either by a complete miss of the vein by failure to introduce the bevel of the needle completely into the vein or by completely transfixing the vein the needle emerging through the posterior wall

Blood may be collected for serological tests either just before the injection through a 3 way stopcock or unattached needle or just after the injection by detaching the syringe or gravity apparatus from the needle and reapplying the tourniquet In the latter case the first drops of blood must be discarded as they may contain enough arsenical to render the serum unfit for serological testing When the injection is completed and the needle withdrawn pressure is applied by the patient over the wound with a sterile gauze sponge

The Technic of Intramuscular Injection

The buttocks are the most suitable muscle masses to utilize in the treatment of syphilis Intramuscular injections should be given into the upper outer quadrant of the buttock If given in the upper inner quadrant one is likely to strike bone or to deposit the injected material near the roots of the sacral plexus from which a troublesome sciatica may result If given in either lower quadrant there is pain on sitting and there is more danger of striking the sciatic nerve or large vessels

The only apparatus necessary is a 2 c c Luer all glass syringe and 18 to 20 gauge needles 1 5 to 2 5 inches long depending on the fatness of the buttock to be injected These instruments should be sterilized by boiling not by alcohol The syringe is filled with the substance to be injected before the needle is attached If the drug to be injected is in suspension in a thick oil or fat the syringe should be filled while hot so that the mass may be liquified

The patient lies face down on a long table thoroughly relaxed and with his feet toed in After preliminary sterilization of the skin with iodine and alcohol the operator draws the buttock down with the left hand toward the patient s heel to fix the tissues The needle may be inserted separately or attached to the syringe A separate insertion is preferable since if a large vessel is struck accidentally blood will flow from the needle In either case however a deep insertion is made with a short sharp stroke the direction of the needle being slightly inward and downward from the vertical

Even though no blood appears at the needle hub aspiration should *always be done as soon as the syringe is attached and before any material* is injected The injection of an insoluble salt especially bismuth in oil suspension into a vein is accompanied always by distressing symptoms of pulmonary embolism and may result fatally If blood does flow from the needle or is obtained even in the smallest amount on the subsequent aspiration the needle must be withdrawn and reinserted at least 1 cm or more from the original puncture

As soon as it is apparent that no blood can be aspirated the injection may be made The suspension or solution should be followed by the injection of 1 c c of air to clean the needle and prevent leakage along the needle track The needle then is withdrawn rapidly and the site of the *injection massaged vigorously* for two or three minutes Alternate buttocks should be used for injection

Painful superficial nodules or lumps usually are due to too shallow injection or leakage along the needle track and are best treated by local heat and massage Large deep indurations may result from a too deep injection With proper care for sterility abscesses should not occur except with sulfarsphenamine With this drug especially in infants a sterile abscess may occur about once in a thousand injections[6]

Lumbar Puncture

Although lumbar puncture properly performed is no more painful than a venipuncture a bungled attempt may mean acute agony for the patient It should not be attempted by the physician unless he is thoroughly qualified by observation and by practice under supervision The average patient will prove cooperative once he is informed first that about 25 per cent of all syphilitics have neurological complications which often can be detected by examination of the spinal fluid long before they are clinically manifest second that the earlier treatment is instituted in such cases the more favorable the ultimate picture and third that a negative spinal fluid is a very good indication that the central nervous system in all probability will not be involved subsequently provided he receives adequate treatment

Two conditions definitely contraindicate spinal puncture One is brain tumor in which because of the increased intracranial pressure withdrawal of fluid from the cord may cause the immediately fatal herniation of the brain stem into the foramen magnum In general puncture should not be performed in patients with choked discs or other signs indicative of increased intracranial pressure Similarly puncture should

not be attempted in patients with recent (less than 2 weeks) subarachnoid or subdural hemorrhage In the second place in patients with intercurrent infections withdrawal of fluid may permit the passage of organisms from blood into the cerebrospinal canal with resultant meningitis

Complications of Lumbar Puncture —About half of the patients who are permitted to go home within a few hours of the puncture develop the so called lumbar puncture headache[97] This usually comes on within 3 to 24 hours and may be excruciatingly severe It is often associated with dizziness nausea and vomiting and is relieved only by lying down It has been suggested (Nelson) that this headache is caused by continued leakage of fluid through the puncture hole in the dura mater Masserman[98] recently has suggested that it is caused not by leakage of fluid and cerebral hypotension but by simple congestion and edema of the central nervous system He recommends the intravenous injection of 250 c c of 20 per cent dextrose The severity of the headache is minimized if a small needle (23 gauge) is used and if the patient goes to bed promptly after the puncture and stays there for 24 to 48 hours

In hospitalized patients if the puncture is performed with the patient lying in his own bed if he lies on his face for 2 or 3 hours afterward and is then allowed to move as he wishes but without raising his head from the pillow for 48 hours puncture headache is relatively uncommon

Very rarely and unpredictably lumbar puncture is followed by a basilar subarachnoid hemorrhage The ocular palsies which sometimes result usually disappear promptly These complications may be due to a rupture of a vessel wall weakened by syphilitic endarteritis

Cisterna Magna Puncture

Puncture of the cisterna magna instead of the lumbar cistern is not followed by headache Moreover medication introduced into the cisterna is correspondingly closer to the brain itself Against these advantages are the real dangers of puncturing the vertebral artery laterally or the medulla if the needle is pushed in too far both errors are fatal Weissenbach[100] estimates from a survey of the literature that there are 2 serious or fatal complications in every 1 000 patients It follows that cisternal puncture should be attempted only by experts and then solely for treatment in cases in which the severity of the complication justifies the danger of the method Certainly it should not be attempted for diagnostic purposes The technic has been described in detail by Ayer[97] and by Spiegel[99]

General Considerations Affecting Treatment

Syphilis is a systemic disease. From the very outset the organism invades the entire body and early or late any organ may be affected seriously in the syphilitic process. The type of treatment used will be determined to a large extent by the particular structures affected and the degree of involvement. It necessarily follows that treatment should never be instituted without first carrying out a careful and complete physical examination. This is essential both in order to detect ophthalmological, cardiovascular, neurological or visceral syphilis and also to rule out the presence of such complicating diseases as tuberculosis, nephritis, diabetes, hypertension and arteriosclerosis. Not only may these diseases modify the clinical course of syphilis but they may decrease seriously the patient's tolerance for the drugs employed. It should never be forgotten that the arsenic, bismuth and mercury compounds used in the treatment of syphilis are potent and dangerous drugs, the therapeutic value of which depends on the fact that they are merely less toxic for the host than they are for the parasite. A complicating disease which upsets that delicate balance in favor of the parasite entails a corresponding modification of the therapeutic regime. Finally, the therapeutic response over a period of years cannot be properly evaluated without the base line furnished by a thorough initial physical examination of each patient.

That age, race and sex play an important part in the clinical course of syphilitic infection has been established clearly. To what extent these factors, as well as the constitutional habitus of the patient, may modify the therapeutic response is one of the unexplored aspects of the disease syphilis.

Two of these factors, age and sex, are clearly important in determining the choice of treatment. The man of 70 with a primary lesion is as infectious as the man of 20, and both must be treated enough to render them permanently non-infectious. The man of 70 with latent syphilis or with a late complication is, however, an entirely different problem than a similar patient 40 years younger. In the one symptomatic relief may constitute a satisfactory result; in the younger patient some more permanent solution is the desideratum. The physical status of the patient, his life expectancy and his infectiousness must all be weighed in deciding on the duration and intensity of the therapeutic regime. Syphilis in women in the childbearing age constitutes a special problem because of the danger of congenital syphilis.

The Treatment of Early Syphilis

It is axiomatic that treatment for primary or secondary syphilis should never be instituted unless the diagnosis has been established beyond question either by the dark field demonstration of spirochetes in a surface lesion or lymph node or by a positive serological test If treatment is begun on suspicion only and if the genital lesion heals within one or two weeks the physician can not conclude that the patient had syphilis, since so many non syphilitic lesions heal spontaneously On the other hand he dare not discontinue treatment lest he precipitate relapse especially neurorecurrence in a patient actually syphilitic The physician is caught on two horns of a dangerous dilemma and so is the patient for he is now condemned to 1 year or more of expensive time consuming and dangerous treatment on the mere suspicion of syphilitic infection *The therapeutic test has no place in the treatment of early syphilis*

Public Health Aspects of Early Syphilis

The chain of infection in syphilis is broken most easily by the adequate treatment of patients with early syphilis by the examination and treatment of those from whom they contracted the disease and by giving them such advice as will prevent their transmitting it in turn before they have been rendered permanently non infectious by treatment Tactfully approached the average patient will cooperate by giving the names and addresses of sexual contacts from whom the disease might have been contracted They should be urged by him to undergo examination and if they do not cooperate the Board of Health should be notified

Secondly those whom the patient might have exposed primarily his immediate family should be examined and the examination including a blood test should be repeated at intervals for a minimum period of 3 months For the first few weeks of treatment the patient s dishes table silver et cetera should be boiled thereafter ordinary cleanliness should suffice Objects which the patient has had in his mouth such as pencils pipes cigarette holders and so on should not be left lying about. He should have his own towels and should sleep alone Kissing and sexual intercourse should be forbidden for the first 6 months of treatment unless the sex partner is infected already and may be resumed thereafter only if he wears a condom Unrestricted intercourse with the possibility of pregnancy should not be allowed unless the patient has remained clinically and serologically cured for a full year after the cessation of

treatment Except for food handlers or patients with occupations which involve close physical contact there is no necessity to stop work and even in such occupations two weeks of treatment with arsphenamine suffice to render the patient non infectious for ordinary contacts and permit the resumption of his daily duties provided of course that treatment i continued

Finally the patient should be apprised of the nature of the disease its seriousness and the necessity for continuous treatment over an 18 to 24 month period Should he be unable to afford treatment by a private physician over this period the physician should aid him to plan less expensive medical care at either pay or free clinics

The Choice of Drug Dose and Method of Administration

Local Treatment — The necessity for a complete medical examination prior to beginning treatment has been discussed already It is useless to attempt to abort the disease by local treatment nor does such local *treatment accelerate healing Spirochetes disappear from open lesions* within a few hours after the injection of arsphenamine and the lesions heal within a few days

Local treatment is however of help in cases of phagedenic ulcer As in the case of chancroids[107] boric acid or hot permanganate (1 1 000) soaks are advised rather than caustics dry heat such as that given by a large electric bulb promotes healing In cases involving a phimotic prepuce the patient should be hospitalized and circumcised

Suppurating inguinal buboes if fluctuant should be nicked the pus expressed and a pressure bandage applied for 24 hours The cavity then should be again expressed and 1 to 2 c c of an antiseptic solution (10 c c each of iodoform guiacol eucalyptol 95 per cent alcohol 30 c c balsam of Peru 100 c c ether) injected with the nozzle of a syringe applied di rectly to the opening no needle should be used A pressure bandage is then reapplied for 48 hours

Necessity for Early Treatment — The welfare of both the community and the individual demand the *early* diagnosis and treatment of early syphilis The epidemiological importance of rendering the patient quickly and permanently non infectious requires no discussion similarly the *ultimate prognosis of the patient himself* varies directly with the time at which treatment is instituted One hundred per cent of seronegative primary syphilis diagnosed by darkfield alone can be cured (permanent clinical and serological negativity) by the best available treatment this drops to 95 per cent in seropositive primary and to 80 to 95 per cent in

secondary syphilis A few days delay in the institution of treatment may mean the difference between a successful and unsuccessful outcome In a large statistical study[101] in which patients were considered without relation to the amount and type of treatment administered the figures in the three groups seronegative primary seropositive primary secondary were all naturally lower, 71 53 and 50 per cent respectively, but the relative order remained the same It is interesting to note that in inadequately treated patients infectious relapse was definitely more common in cases of primary syphilis than in patients who had already developed secondary lesions perhaps because in the latter group the body s own defenses had developed to a greater degree before being halted by treatment On the other hand late relapse or progress in the central nervous system and cardiovascular apparatus were more common in inadequately treated cases of secondary syphilis presumably because of the more extensive invasion of the organisms into these systems before the institution of treatment

The Choice of Drugs[103] — The choice of drugs for use in the treatment of early syphilis lies between arsphenamine neoarsphenamine and mapharsen Compared to these bismarsen is of relatively weak treponemicidal activity sulfarsphenamine apparently is followed by a higher incidence of dermatitis and blood dyscrasia silver arsphenamine used in conjunction with bismuth may cause argyria While mapharsen has been in use for too short a time to enable any definitive comparison on the basis of ultimate outcome its early results are comparable to those of arsphenamine and neoarsphenamine As between arsphenamine and neoarsphenamine the material of the Cooperative Clinical Group[101] (Table XV) indicates the definite superiority of arsphenamine Not

TABLE XV

ARSPHENAMINE VERSUS NEOARSPHENAMINE IN EARLY SYPHILIS (2889 CASES FOLLOWED FOR 6 MONTHS OR LONGER)

(Data of Cooperative Clinical Group)[1] *

Scheme of treatment	Arsphenamine		Neoarsphenamine	
	Results satisfactory	Relapse (all forms) or serological resistance	Results satisfactory	Relapse (all forms) or serological resistance
Continuous	35 9	1- 4	20 3	16 4
Intermittent	21 5	0 4	17 6	23 1
Irregular	13 1	45 1	14 3	46 [illegible]

* Leaving out of consideration the total amount of treatment administered

only did a larger proportion of patients give satisfactory results 36 as against 20 per cent for neoarsphenamine but a smaller proportion 12 as against 16 per cent relapsed clinically or remained reagin fast The superiority of arsphenamine was no longer manifest with uncooperative patients who refused to come regularly but where the cooperation of the patient is assured the best treatment of early syphilis still demands the use of arsphenamine

Dosage — It is important to attain maximum treponemicidal action from the outset Accordingly the first three treatments should be comparatively large 0 1 gm arsphenamine and 0 15 gm neoarsphenamine for each 25 pounds of body weight However regardless of weight the maximum dose should not exceed 0 6 gm arsphenamine 0 9 gm neoarsphenamine or 0 06 gm mapharsen After the first three injections the average dose in men is 0 4 gm arsphenamine or 0 75 to 0 9 gm neoarsphenamine The corresponding doses in women are 0 3 gm arsphenamine and 0 6 to 0 75 gm neoarsphenamine If mapharsen is used the average dose for men is 0 060 gm for women 0 040–0 050 gm and it is probable because of the more rapid excretion of this drug that in early syphilis injections should be given twice rather than once weekly There is no adequate evidence that either the immediate constitutional reactions of therapeutic shock or the late serious reactions of jaundice or dermatitis are less common or less serious if smaller doses are used Moreover smaller doses may not suffice to effect even a rapid surface sterilization of open lesions

Bismuth Versus Mercury — A definite comparison between the efficacy of these two drugs in the treatment of early syphilis is rendered difficult by the fact that they are used in conjunction with a far more potent drug arsphenamine Although the data of the Cooperative Clinical Group (Table XVI) indicate a definite superiority of bismuth with respect to both the percentage of serologic reversal and the incidence of infectious relapse other studies[104] indicate but little difference

Simultaneous or Separate Administration of Arsenic and Heavy Metals — The simultaneous administration of bismuth or mercury along with arsenic might increase the potential toxicity of the arsenic for the liver and kidney by causing renal damage and thus retarding excretion Theoretically also the continuous simultaneous treatment with both arsenic and bismuth or mercury might cause the organisms to become resistant to both metals simultaneously and the development of such drug fastness would necessitate an altogether undesirable rest period in order that the tolerance might disappear

The decreased incidence of neurorecurrence which Harrison[104] cites

in favor of the simultaneous method of treatment as against the use of alternating courses of arsenic and bismuth is not confirmed by the data of the Cooperative Clinical Group. Nevertheless a few simultaneous injections at the very outset of treatment would not increase significantly the risk of toxic reactions and might serve to minimize the risk of this complication.

Continuous Versus Intermittent Treatment.—Keidel in this country (1916–1917)[105] and Almkvist independently abroad conceived of a plan of continuous treatment whereby courses of arsphenamine consisting of 6 or 8 weekly injections would be alternated with similar courses of mercury or bismuth. The interval rest period thus would be eliminated and the spirochetes, instead of entering on a period of multiplication and dissemi-

TABLE XVI

RELATIVE EFFICIENCY OF BISMUTH AND MERCURY IN EARLY SYPHILIS AS REFLECTED IN WASSERMANN REVERSAL AND INFECTIOUS RELAPSE

Treatment		Wassermann reversal		Infectious relapse	
		Total patients treated	Percentage showing Wassermann reversal within 12 months	Total patients treated	Percentage incidence of infectious relapse
Arsphenamine	plus bismuth	37	55.9	608	3.6
	plus mercury	466	44.7	1117	9.8
Neoarsphenamine	plus bismuth	48	54.6		
	plus mercury	65	46.8		

Omitting consideration of the method (continuous, intermittent, etc.) by which treatment was given or of total amount of treatment.

nation during that interval unchecked either by drug or by the host's defense mechanism, instead would be under continuous attack, first by arsenic, then by heavy metal and then again by arsenic. The premises on which that continuous method was based and the improvement in therapeutic results obtained by it have been confirmed abundantly. The results of the Cooperative Clinical Group summarized in Table XVII show how great that margin of superiority is over either the intermittent method, i.e., courses of arsenic and mercury combined alternating with rest periods, the intensive Pollitzer method which consists of a few massive injections at comparatively short intervals, or the haphazard treatment obtained by patients who receive injections at irregular intervals. The differences in the results obtained with early secondary

syphilis were even more pronounced than is indicated in the table With continuous treatment satisfactory results were obtained in 81 per cent of the cases with intermittent treatment in 61 per cent with irregular treatment in 30 per cent while intensive treatment gave satisfactory results in only 12 per cent Corresponding to the clinical results 53 per cent of the patients treated by the continuous method had become seronegative in three months contrasted with 21 per cent by the intermittent method and none by the irregular method after 12 months the

TABLE XVII

THE OUTCOME IN VARIOUS TYPES OF EARLY SYPHILIS AS COMPARED WITH THE CHARACTER OF TREATMENT IN PATIENTS OBSERVED FOR 2 OR MORE YEARS

(Data of Cooperative Clinical Group)[11]

Type of treatment	Total cases treated	Satisfactory clinical† results obtained per cent
Continuous	172	9[illegible]
Intermittent	595	65 0
Irregular	546	33 3
Intensive	47	23 4
Total	1360	52 7

Continuous — Uninterrupted treatment with an arsphenamine and a heavy metal usually administered in alternation

Intermittent — Treatment interrupted by short rest intervals of 1 month or more purposeful or not

Irregular — Treatment absolutely irregular no regular system consistently or even approximately being followed

Intensive — An intensive arsphenamine phase (3–4 injections in 3–8 days) alternating with a more or less prolonged heavy metal course The so-called Pollitzer system

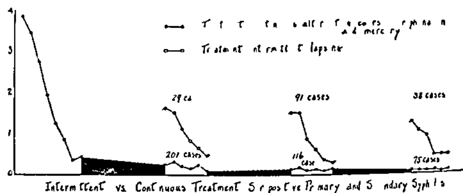
† *Satisfactory results* — All patients with reinfection all those satisfactorily completing a year of probation (no lesions of syphilis repeated negative blood Wassermann tests *negative cerebrospinal fluid normal physical examination)* *a few patients who had* entered upon but not yet completed the probationary year with all findings negative

figures were 61 8 37 3 and 4 7 per cent respectively Conversely the incidence of persistent serological positivity regin fastness was 11 37 and 68 per cent in the patients treated by the continuous intermittent and irregular plans respectively

This striking difference in treatment results is also illustrated in Fig 1 in which the composite Wassermann curve of patients treated by the intermittent method is compared with that on a similar group treated by the continuous method Despite the inaccuracy of the method of averaging the Wassermann results[43] the chart clearly shows the tendency of the

Wassermann reaction to relapse during the rest period indicative of a re-dissemination of the syphilitic infection and multiplication of the organisms as originally postulated by Keidel and by Almkvist while the use of alternating courses of arsenic and heavy metal prevents that serological relapse and makes for a smoothly progressing decrease in serological positivity indicative of a similarly progressive eradication of infection

The study of Martenstein[106] on treatment results in early syphilis in five countries confirms the thesis that continuous treatment with alternating courses of arsphenamine and heavy metal is the method of choice Although satisfactory results were obtained also in patients treated with



Legend to Fig 1

The Composite Wassermann Curve of Patients Treated by the Intermittent and by the Continuous Methods of Treatment (after Moore[4])

The routine serologic reports of 4+ 3+ 2+ 1+ and 0 obtained in the course of the two types of treatment were averaged to obtain the points plotted in the figure Although the average so obtained is admittedly inaccurate and the results of little or no *absolute* significance[41] there is a statistically significant qualitative difference in the serologic response obtained by the two methods of treatment

courses of simultaneous arsenic and heavy metal alternating with *short* rest periods the intramuscular stores of heavy metal ensured essentially continuous treatment in that group as well

• *Massive Arsenical Treatment of Early Syphilis* — Recently Chargin Leifer and Hyman[107] have restudied the effect of massive doses of neoarsphenamine (2 4 to 5 gm) administered by the drip method within 4 to 5 days Although they considered their initial clinical and serological results satisfactory the method still is wholly experimental Moore[108] enjoins caution in the premature acceptance of a treatment plan so closely related to a method of proved inefficiency i e the intravenous injection of comparatively large doses repeated at intervals over a relatively short period of time

The Fever Therapy of Early Syphilis

The use of artificially induced fever in the treatment of early syphilis has been discussed recently by several workers[109] All are agreed that hyperpyrexia alone does not suffice there is however some evidence that if the fever is supplemented by a short course of arsphenamine and bismuth initially satisfactory results are obtained However the method is too recent and the number of cases treated too small to justify any definitive evaluation[110]

Duration of Treatment

The results of Table XVIII indicate that the percentage of patients

TABLE XVIII

THE RESULTS IN EARLY SYPHILIS AS AFFECTED BY THE DURATION OF TREATMENT

(Moore and Kemp)

Amount of treatment	Total patients	Per cent of probable cure ncluding rein fection	Relapse (sero logical or clin ical)
1–8 doses arsphenamine no heavy metal	196	10 8	89
8–14 d ses arsphenamine plus interim mercury	69	3 1	6 9
14– o doses ar phenamine plus inter m mercury	46	56 6	43 4
1 or more doses arsphenam e plus interim mercury	,1	,8 8	21 2

who have a satisfactory clinical outcome increases directly with the duration of treatment The ideal duration of treatment in various types of syphilis for optimum results may be defined as follows[6]

Seronegative Primary Syphilis — Twelve months provided the blood Wassermann remains negative throughout If treatment is to be as short as this the blood Wassermann must be tested at the time of every injec tion of the arsphenamine course in order to rule out the presence of a provocative Wassermann If this cannot be done 15 to 18 months of treatment should be given

Seropositive Primary and Early Secondary Syphilis — Fifteen to 18 months The blood Wassermann usually becomes and remains negative by the start of or during the second arsphenamine course Treatment should be continued for one year after this time

Delayed or Late Secondary Syphilis — Eighteen months to 2 years. This is more than the amount usually necessary to render the patient non-infectious or to insure against infectious relapse. On the average a minimum of 20 doses of arsphenamine in 7 to 8 months of treatment is necessary to effect this result. In the occasional patient, however, a much longer time may be necessary.[6]

The Significance of the Serological Tests in the Treatment of Early Syphilis[111]

In patients under treatment for early syphilis it suffices to do a blood Wassermann or flocculation test in the middle and at the conclusion of

TABLE XIX

THE RELATIONSHIP OF WASSERMANN FASTNESS AND SPINAL FLUID ABNORMALITIES IN EARLY SYPHILIS

(Data of Cooperative Clinical Group)[11]

Cerebrospinal fluid	Total patients	Per cent Wassermann fast for 6 months or longer
Normal	1 522	16 0
Group Ia cells 6 or over all other findings negative	146	15 8
Group Ib cells 5 or over excess protein Wassermann and colloidal test negative	195	22 6
Group II cells and protein + or − Wassermann partial positive colloidal test + or −	228	45 6
Group III paretic formula	26	4- 3

the first course of arsphenamine injections and thereafter at the beginning of each course of arsenical. Treatment should never be stopped when the serum test becomes negative; this negativity does not imply cure and the cessation of treatment may lead to dangerous clinical relapse. The treatment of early syphilis should continue for at least one year after the Wassermann reaction becomes negative.

Approximately 85 per cent of patients with early syphilis eventually do become negative under adequate treatment by the continuous method. A considerable proportion of those with persistently positive serological tests, "reagin fast," are found to have abnormal spinal fluid findings indicative of central nervous system involvement. Conversely the chances of serological "cure" are diminished if the spinal fluid is found to be abnormal and in proportion to the degree of abnormality (Table XIX).

No explanation has been offered for the reagin fastness of patients with early syphilis with no demonstrable central nervous system involvement nor are there any convincing data as to whether the persistently positive test is necessarily of serious prognostic significance

One not infrequently observes in patients rendered seronegative by treatment a subsequent reappearance of positive tests If this occurs within a few weeks of the first negative report it may reflect minor and unimportant changes in the reagin content of a serum which is almost but not quite reagin free Equally possible the unavoidable variations in the day to day sensitivity of the laboratory test may cause the same serum to be seronegative on one occasion and seropositive on another In either case this pseudo relapse is of no clinical significance and the patient usually proceeds under continued treatment to complete and permanent seronegativity

On the other hand a definite and persistent relapse of the blood tests to positive occurring early after an interval without treatment is of serious significance It often is associated with clinical relapse and even in the absence of such clinical manifestations probably is indicative of a redissemination of infection In such a case if the positive test is confirmed treatment must be reinstituted as if the patient were a new case of early syphilis and must be continued for a year after the serological tests become negative

Clinical Relapse in Early Syphilis

Adequate treatment affords 95 per cent protection against early infectious relapse Nevertheless about 4 to 7 per cent of the patients with early syphilis no matter how well treated will proceed to develop late cardiovascular visceral or central nervous system syphilis The early recognition of spinal fluid abnormalities and the institution of appropriately modified treatment may serve to decrease the late neurological complications

After inadequate treatment on the other hand relapse is so common as almost to justify the statement that a little treatment is worse than none Two types of relapse in inadequately treated syphilis may be distinguished early infectious and late Approximately half of the cases of early infectious relapse (mucocutaneous ocular or neurorecurrence) develop within 6 months after the cessation of treatment and 91 per cent within two years The late evidences of inadequately treated syphilis on the other hand require years for their appearance the average time interval varying between the average 29 months of benign late syphilis the 3–10

years of late central nervous system syphilis and the 5 to 25 years of cardiovascular syphilis. The time required for the evolution of these complications often is less than that necessary in the untreated patient in whom benign manifestations usually do not develop for 3 to 7 years tabes or paresis for 12 to 18 and cardiovascular syphilis for approximately 20. It is an interesting speculation whether this may not be due to the fact that the abortive treatment of early syphilis by cutting short the evolution of the body's own immune defenses thereby promotes or at least accelerates these late manifestations.

Spinal Fluid Examinations in Early Syphilis[111]

The first spinal fluid examination should be performed 5 to 6 months after the beginning of treatment. If negative the test need not be repeated until after 1 year's probation has elapsed without treatment provided that the patient in the meantime does not develop clinical evidence of neurological involvement and provided also that there is no other clinical or serological relapse. If the patient's spinal fluid examination is negative after the year's probation no further punctures are necessary and the patient can be assured that he will not develop tabes or paresis.

The changes in treatment necessitated by a positive spinal fluid will be discussed in a following section.

The Periods of Probation and Observation

In the uncomplicated case of early syphilis which has been treated continuously treatment may be stopped after a full year of serological negativity. If however treatment has been irregular it should be continued regardless of the result of the blood test, until the patient has received five full courses each of an arsenical and a heavy metal 30 injections. If the patient is reagin fast treatment should be continued for a minimum of 2 years equivalent to a minimum of eight courses 48 injections each of an arsenical and a heavy metal.

Following the cessation of treatment the patient should be placed on probation but under close observation for a year. Blood tests should be taken every 2 months. If at the end of the year the patient shows no clinical or x ray evidence of cardiovascular involvement if the spinal fluid is negative, and if the blood tests have been consistently negative he may be regarded as probably cured. Nevertheless blood tests should be continued at lengthening intervals and annually after the third year. Finally there should be a clinical examination at least as often as

every two years to ensure the early recognition of late serious cardiac or neurological involvement in the rare case. If the patient remains clinically and serologically negative for 5 years after the cessation of treatment he is likely to remain so for the rest of his life.

A scheme of treatment for uncomplicated early syphilis, giving a bare outline of the basic principles discussed in this section, is given in Table XX.

Complications In the Treatment of Early Syphilis

Treatment of Early Syphilis in Infants and Young Children. — Infants may develop extragenital chancres, usually on the lips, from contact with lesions on the nipples of nursing mothers. More frequently older children may acquire syphilis either through genital or extragenital infection.

The principles of the treatment of early acquired syphilis in children are exactly the same as in adults, i.e., maximum treponemicidal attack, continuous treatment without rest intervals, and prolonged treatment based on serological control of blood and cerebrospinal fluid. The choice of arsenical drugs depends on the ease of their administration. In infants and young children sulfarsphenamine is the drug of choice since it may be given by the intramuscular route. Fortunately it is better tolerated by children than by adults and such complications as dermatitis, nephritis and blood dyscrasias need not be especially feared. In older children with available veins, to whom intravenous treatment may be given without too great physical struggle, mapharsen or neoarsphenamine may be used in place of arsphenamine, since they are easier to give (small needle, small bulk of fluid, fewer mild reactions) and since the cooperation of the child and its parents should be maintained so far as possible by minimizing the pain and discomfort of treatment. The arsphenamine product selected should be used at the start of treatment as in adult patients. There is no need for preparatory heavy metal courses.

Children tolerate arsenical drugs in general in higher dosage and with fewer mild or grave reactions than do adults. Full advantage may be taken of this fact. The dosage of either sulfarsphenamine or of neoarsphenamine may begin at a level of 15 mgm. per kilo of body weight, increasing promptly to 25 mgm. per kilo. Each course of arsenical therapy may consist of 8 injections. Mapharsen may be used in a dosage of 1 mgm. per kilo of body weight, but with this drug courses probably should consist of 10 to 12 injections.

Bismuth salicylate may be used as interim treatment just as in

TABLE XX

A SCHEME OF TREATMENT FOR EARLY SYPHILIS

Day or week	Arsphenamine	Interim treatment	Blood Wassermann reaction	Remarks
Day				
1	0·3–0·6	Bismuth 0·[illegible] gm simultaneously with first 4 doses of arsphenamine	I	Arsphenamine dosage for first 3 injections at level of 0·1 gm for each 25 pounds body weight. Average subsequent dosage 0·4 gm men, 0·3 gm women. In average patient all lesions heal rapidly and blood Wassermann reaction becomes negative during first course. If arsphenamine *cannot be used* substitute 8 to 10 doses 0·3 gm silver arsphenamine or 10 to 12 maximum doses 0·9 gm neoarsphenamine. This applies also to subsequent courses. If mapharsen is used give 16–20 biweekly injections per course
5	0·3–0·6			
10	0·3–0·6			
Week				
3	+			
4	+			
5	+			
6	+			
7	+			
8		Bismuth 4 doses 0·2 gm and K I or Ung Hg and K I	I	If mercury is used note overlap of 1 week at end of first and start of second arsphenamine courses. No overlaps necessary with bismuth. At this point a few days without treatment may be dangerous. Neurorecurrence
9				
10				
11				
12	+		I	Arsphenamine starts, bismuth stops. Watch for provocative Wassermann reaction after first dose of arsphenamine
13	+		I	
14	+			
15	+			Try to prevent short lapses in treatment especially at this early stage
16	+			
17	+		I	
18–23		Bismuth [illegible] doses or Ung Hg and K I		Bismuth is better than mercury. Use it if possible. Examine cerebrospinal fluid routinely at about this time
24	+			
25	+			
26	+			
27	+			
28	+			
29	+			

TABLE XX — Continued

Day of week	Arsphenamine	Interim treatment	Blood Wassermann reaction	Remarks
30-3		Bismuth 8 doses or Ung Hg and K I	1	Mercury inunctions may *be substituted for bismuth if* patient's finances or occupation (travelling salesman etc) demand it
38	+			
39	+			
40	+			
41	+			
4	+			
43	+		1	Patients with seronegative primary syphilis may cease *treatment here if blood Wassermann reaction always* has been negative
44-53		Bismuth 10 doses or Ung Hg and K I		Note that bismuth or mercury courses are gradually getting longer — 4 6 8 and now 10 weeks
54	+		1	The average seropositive primary or early secondary patient should have at least 5 courses of arsphenamine
55	+			
56	+			
5	+			
58	+			
59	+		1	
60-( )		Bismuth 10 doses or Ung Hg and K I		It is safer to finish treatment with bismuth or mercury rather than with arsphenamine
70-122		No treatment	6 12	Blood Wassermann every month if possible at least *every other month*
1 3	Complete physical and neurologic examination spinal puncture and if possible fluoroscopic examination of cardiovascular stripe Thereafter yearly physical examinations blood Wassermann every 6 to 12 months *If the two spinal fluid examination* above are negative this need not be repeated			
Probation				

adults The average dosage is measured on the basis of body weight 2-4 mgm per kgm Or if the child's parents can be trusted to cooperate mercury by inunction may be substituted with advantage since this involves no pain to the child For an infant a daily 1 gm rub of 50 per cent U S P mercury ointment may be given with proportionately larger dosage up to 4 gm for older children Routine examination of the cerebrospinal fluid should be carried out as in adults[6]

Treatment of Early Syphilis in Elderly Patients — In patients who acquire syphilis at e g the age of 60 the normal life expectancy is so short that there will not be time to develop the late complications The goal of treatment is simply to render the patient non infectious and to prevent infectious relapse or neurorecurrence To achieve this end although treatment still is continuous neoarsphenamine, 0 3 to 0 6 gm or mapharsen 0 04 gm may be used instead of arsphenamine and treatment may be discontinued after one year

Treatment of Early Syphilis Complicated by Pregnancy — If the infection is discovered before the fifth month of pregnancy the patient should be given the usual treatment with alternating courses of arsphenamine and bismuth If the patient is infected within the last 3 months of pregnancy or if the infection is not discovered until then treatment must be more intense in order to minimize the chances of a syphilitic baby and arsphenamine should be given weekly until delivery If lesions of early syphilis are discovered just before term one or more injections of an arsphenamine should be given to safeguard the obstetrician and to minimize the chance of the fetus being infected during its passage through the birth canal

Treatment of Early Syphilis Complicated by Arsphenamine Resistance — In about 0 2 per cent of patients with early syphilis arsphenamine fails to cause the disappearance of the organisms from open lesions In others the lesions of early syphilis may heal during the administration of the arsphenamines only to relapse as soon as heavy metal is begun These relapses may involve structures not originally involved e g central nervous system or ocular lesions and usually heal promptly when the arsphenamines are resumed

It is an open question whether this arsphenamine resistance is due to infection with a drug fast strain of *T pallidum* or whether it is due to a peculiarity in the host In favor of the former is the drug tolerance which some workers have induced in cultures of non pathogenic *S pallida*[113] and in syphilitic rabbits[114] by sub lethal and sub curative doses of arsphenamine However the latter observation has not been confirmed[115] Moreover if rabbits are inoculated with organisms from

arsphenamine resistant patients the experimental disease usually is cured readily by arsphenamine[116] These data coupled with the fact that drug resistance is particularly likely to occur in patients with seronegative secondary syphilis or with low reagin titres (Moore and Kemp[111]) suggests that the altered reactivity of the patient may be of primary importance[115 117]

Resistance to the arsphenamines sometimes is specific for one member of the group in which case the lesions heal if e g neoarsphenamine is changed to silver arsphenamine In the great majority of cases it is peculiar to the arsphenamines and the lesions heal with bismuth or mercury

The handling of a case with arsphenamine resistant syphilis therefore consists in (1) changing the arsphenamine (2) intensifying the treatment in the sense that larger doses of the arsenical are employed and are administered twice weekly instead of weekly and (3) giving bismuth intramuscularly simultaneously with the arsenical Potassium iodide may be given orally in daily doses of 8 to 10 gm At least ten such combined treatments should be given before the course of heavy metal alone is begun Subsequent treatment should be continuous with gradually decreasing intensity until the person has remained clinically well and seronegative for a full year In the occasional patient who does not respond to this intensified treatment in whom the lesions either fail to heal or relapse when the arsenical is discontinued malaria followed again by arsphenamines and heavy metal will produce satisfactory results

Treatment of Early Syphilis Complicated by Treatment Reactions — Post arsphenamine Jaundice — Treatment should be discontinued during the acute phase of the illness 10 to 14 days Heavy metal treatment preferably bismuth then is instituted Arsphenamine usually may be resumed 2 to 3 months after the jaundice disappears beginning with a small dose (0 05 gm) and increasing week by week (0 1 0 15 0 2 et cetera) until the average dose is reached Sclerae urine and blood should be watched carefully and if jaundice reappears arsphenamines must be permanently discontinued

Arsphenamine Dermatitis and Blood Dyscrasias — As already indicated arsphenamine dermatitis if actually caused by drug sensitization contraindicates the further use of the trivalent arsenicals This is true also of the blood dyscrasias Sensitization to the trivalent arsphenamines does not however usually extend to the pentavalent tryparsamide which fortunately is utilizable in the event of complicating neurosyphilis

Heavy Metal Treatment of Early Syphilis — Where the arsphenamines cannot be given the physician must rely on heavy metals alone prefer

ably courses of insoluble bismuth injected intramuscularly as indicated in Table XXI, alternating with courses of mercury by inunction. The duration of treatment will be determined to a large extent by the amount of arsenical which the patient had received before it had to be discontinued. Since the incidence of asymptomatic neurosyphilis is increased under bismuth alone, examination of the spinal fluid is particularly important and it should be retested at the end of the second and fifth years after treatment.

Management of Early Syphilis with Associated Visceral Lesions of Syphilis. — The presence of syphilitic hepatitis[118] fortunately is rare and requires extremely cautious treatment beginning with a small dose of

TABLE XXI

SUGGESTED OUTLINE OF TREATMENT FOR EARLY SYPHILIS IF SOLE RELIANCE MUST BE PLACED ON THE HEAVY METALS

Amount of arsphenamine given before the reaction	Duration of continuous treatment with alternating courses of bismuth and mercury	
1–6 doses	3–5 years	Remember that tryparsamide may be added to this scheme if the patient has clinical evidence of neurosyphilis or an abnormal spinal fluid
7–12 doses	2–3 years	
13–18 doses	$1\frac{1}{2}$–$2\frac{1}{2}$ years	
19–24 doses	9–18 months	
More than 24 doses	6–9 months	

neoarsphenamine 0.1 gm. or mapharsen 0.01 gm. given biweekly in gradually increasing amounts. On days when the arsenical is not given a soluble mercury salt, e.g., mercury succinimide, may be given intravenously in a dose of 0.01 to 0.02 gm. The jaundice occasionally observed in early syphilis also enjoins initial caution in treatment; usually, however, the jaundice disappears after several small doses of arsphenamine and average therapeutic doses then may be given.

Whether the clinical picture is that of an acute glomerular nephritis or that of a lipoid nephrosis, *syphilitic nephritis* is a serious complication which necessitates hospitalization and careful treatment. Heavy metals should not be given but small doses of arsphenamine (0.1 gm.) should be given two or three times weekly. Recovery usually is rapid and complete.

In some cases of early syphilis there may be *fever* as high as 103° F. This does not contraindicate the usual energetic treatment and although there may be a further rise in temperature of 12 to 24 hours duration after treatment, usually it falls promptly to normal.

The treatment of early neurosyphilis is discussed elsewhere.

Management of Treatment Complicated by Other Diseases

Pulmonary Tuberculosis[11] — Although the patient must be rendered non infectious and infectious relapse must be prevented the danger of lighting up the tuberculous process by treatment is a very real one and demands that these ends be accomplished by the mildest possible treatment Small doses of neoarsphenamine 0 3 to 0 45 gm or mapharsen 0 02 to 0 03 gm and intervening courses of bismuth in half doses 0 1 gm subsalicylate should suffice Iodides should not be given

Rheumatic Heart Disease — The treatment of the syphilitic patient with rheumatic heart disease will be determined by the severity of his cardiac complication If his life expectancy on that score is good then he must be treated energetically for early syphilis substituting neoarsphenamine or mapharsen for arsphenamine On the other hand if his cardiac reserve is low and his prognosis poor he should be given only that amount of treatment which will render him non infectious e g courses of 0 1 to 0 3 gm neoarsphenamine or 0 020 to 0 040 gm mapharsen and mercury by inunction

Essential Hypertension and Diabetes — Neither of these conditions is a contraindication to intensive treatment In the case of the former the urine should be examined monthly to guard against renal damage

Exophthalmic Goitre — The thyroid condition should be treated surgically as promptly as possible Until convalescence is complete small doses of arsphenamine 0 1 to 0 45 gm or mapharsen 0 01 to 0 03 gm must suffice

Nephritis — Treatment with small doses of arsphenamine 0 1 gm or neoarsphenamine 0 15 gm two or three times weekly will establish within a few weeks whether nephritis in a case of early syphilis is due to syphilitic nephritis in which case recovery is rapid or whether it is due to some other process If the latter the intensity of treatment must depend on the degree of renal involvement and the probable prognosis Although mercury should not be used in such patients mild treatment with arsphenamine and bismuth throws but little additional load on the kidneys

If albumen and casts suddenly appear in considerable amounts in a previously normal urine treatment should be discontinued If they disappear promptly treatment may be resumed cautiously within three to four weeks Mild albuminuria a trace to a heavy trace and cylindruria a few casts in an entire field are common during any form of antisyphilitic treatment and usually may be disregarded

ably courses of insoluble bismuth injected intramuscularly as indicated in Table XXI alternating with courses of mercury by inunction The duration of treatment will be determined to a large extent by the amount of arsenical which the patient had received before it had to be discontinued Since the incidence of asymptomatic neurosyphilis is increased under bismuth alone examination of the spinal fluid is particularly important and it should be retested at the end of the second and fifth years after treatment

Management of Early Syphilis with Associated Visceral Lesions of Syphilis — The presence of syphilitic hepatitis[118] fortunately is rare and requires extremely cautious treatment beginning with a small dose of

TABLE XXI

SUGGESTED OUTLINE OF TREATMENT FOR EARLY SYPHILIS IF SOLE RELIANCE MUST BE PLACED ON THE HEAVY METALS

Amount of arsphenamine given before the reaction	Duration of continuous treatment with alternating courses of bismuth and mercury	
1–6 doses 7–12 doses 13–18 doses 19–24 doses More than 24 doses	3–5 years 2–3 years 1½–2½ years 9–18 months 6–9 months	Remember that tryparsamide may be added to this scheme if the patient has clinical evidence of neurosyphilis or an abnormal spinal fluid

neoarsphenamine 0 1 gm or mapharsen 0 01 gm given biweekly in gradually increasing amounts On days when the arsenical is not given a soluble mercury salt e g mercury succinimide may be given intravenously in a dose of 0 01 to 0 02 gm The jaundice occasionally observed in early syphilis also enjoins initial caution in treatment usually however the jaundice disappears after several small doses of arsphenamine and average therapeutic doses then may be given

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The treatment of early neurosyphilis is discussed elsewhere

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The Treatment of Late Syphilis

General Considerations — In early syphilis an adequate amount of treatment will in the great majority of cases not only heal lesions and ensure against progression or relapse but actually will effect biological cure in the sense that the infection is eradicated and the patient barring reinfection remains permanently seronegative and clinically well Since the therapeutic clinical picture is so uniform the response so regular and the patients usually in such good general condition treatment may be more or less standardized

In late syphilis on the other hand such biological cure usually cannot be achieved Complete eradication of infection accordingly is not the goal of treatment Moreover the syphilitic process may involve any organ and often disturbs vital functions The therapeutic response likewise is unpredictable It follows that the therapeutic regime cannot be standardized but must be adjusted carefully to the individual case In general the proper treatment of late syphilis is that treatment which considered in the light of his general condition and degree of syphilitic involvement (a) may be given without causing further damage (b) will cause the healing of lesions and symptomatic relief and (c) will prevent either relapse of the inflammatory process or the development of new complications

The Treatment of Latent Syphilis*

Latency in syphilis may be either (a) serological in that the blood and spinal fluids are negative in a patient known to be syphilitic, (b) biological in that the organism living in perfect symbiosis with its host is causing no inflammatory reaction (c) clinical in that the syphilitic infection is not recognizable on clinical examination In general when one speaks of latent syphilis one refers to clinical latency in which a careful physical examination *including spinal puncture* fails to reveal cardiovascular neurological or indeed any objective manifestation of syphilis and in which the diagnosis rests on either a positive blood test definite history of syphilitic infection or the birth of a syphilitic child The italics are justified by the fact that approximately 15 per cent of patients with apparently latent syphilis actually have asymptomatic neurosyphilis revealed only by a spinal puncture

The importance of latent syphilis is best illustrated by the fact that of 10 000 syphilitic patients who presented themselves for treatment at a

* Largely based on the study of the Cooperative Clinical Group[120]

large clinic approximately ½ of the women and ⅓ of the men fell into this category[121] It is of interest that almost half of these could give no history of infection Granted that this may reflect either a lapse of memory or a relatively insignificant initial lesion it seems entirely likely that a considerable number were truly cases of symptomless infection The frequency of latent syphilis in general and of infectious latent syphilis in particular alone justifies the routine performance of serological tests on all patients whether seen in private practice or in hospitals

Prognosis of Latent Syphilis in Relation to the Necessity for Treatment

Although other pathologists cannot confirm fully the high incidence of pathological alterations as found by Warthin[122] in cases of latent syphilis it is nevertheless apparent that there must often be pathological changes not appreciable by the relatively crude tests of the objective clinical examination but which in the absence of treatment may progress subsequently to become clinically recognizable As indicated in Table XXII

TABLE XXII

The Probable Outcome of Untreated Latent Syphilis

Outcome	Approximate per cent of patients in whom specified results may be expected to develop
Spontaneous cure (blood Wassermann and cerebrospinal fluid negative no lesions)	25–35
Infection remains latent (blood Wassermann positive cerebrospinal fluid negative no lesions)	25–35
Late syphilis (skin mucosa osseous)	10–15
Cardiovascular syphilis	10–15
Neurosyphilis	1–2
Visceral syphilis other than cardiovascular	0 5–1

such progression may be expected in approximately 20 to 30 per cent of clinically latent patients who have had their infection for 4 years or longer However in only half of these is there serious cardiovascular *involvement and the chances of developing neurosyphilis are small* indeed These figures on the prognosis of late latent syphilis are not to be confused with the prognosis of syphilitic infection in general Approximately 50 per cent of *untreated syphilitics will develop some late lesion* and in 25 per cent of these that lesion will be either incapacitating or fatal

In patients with early latent syphilis i e infection of two years duration or less the chances of late serious complications probably are greater and the possibility that such patients may be infectious for others is another compelling reason for treatment

Type and Amount of Treatment for Latent Syphilis

Since patients who have had their infection for four years or longer probably have developed true latency in the sense that they have developed maximum immunological resistance to reinfection or infectious relapse there is no longer an imperative need for continuous treatment In actual fact the studies of the Cooperative Clinical Group indicate that the results obtained with continuous and with intermittent treatment in late latent syphilis are entirely comparable On the other hand in early latent syphilis i e of less than 4 years duration the patient s immunity is not fully developed For such patients as in cases of early syphilis continuous treatment accordingly is necessary and the cessation of treatment even if only temporary predisposes to serological and perhaps infectious relapse In either case the drug of choice is neoarsphenamine rather than arsphenamine and mapharsen with its lower incidence of treatment reactions eventually may prove to be more desirable than either The minimum number of injections should be at least twenty As in early syphilis bismuth largely has replaced mercury and recent studies[170] indicate that the results in latent syphilis are somewhat better if relatively more heavy metal is employed than in early syphilis

The Results Achieved by the Treatment of Latent Syphilis

Clinical Improvement — Frequently a patient who had not been conscious of feeling badly reports a few weeks after starting treatment that he now feels very much better He has more energy, tires less easily has an improved appetite sleeps better and such vague discomfort or malaise as he may have had has disappeared Indeed he often looks better insofar as he gains a little weight and his color is improved This change is more than the tonic effect of arsenical treatment experienced even by non syphilitic patients it represents apparently genuine improvement in the systemic infection and is a sustained gain

End Results — The most important variable affecting the end results achieved in the treatment of latent syphilis is the duration of the infection As shown in Table XXIII the earlier the infection is recognized the larger is the proportion of patients in whom after the completion of

treatment and after a probationary period the patient remains clinically well and seronegative

The 35 to 50 per cent of patients with unsatisfactory results indicated in that table represent largely Wassermann, i.e., reagin fastness as only 4 to 5 per cent of the patients in either group developed clinical relapse In one third of these the relapse was benign in type In another third of the relapsing patients although the cardiovascular or neurological system was involved the lesions were mild and rarely incapacitating With passing time the proportion of reagin fast patients in the treated

TABLE XXIII

THE DURATION OF INFECTION AS INFLUENCING THE OUTCOME OF TREATMENT IN LATENT SYPHILIS

(Material of Cooperative Clinical Group)[30]

Stage of latency	Total patients	Per cent with		
		Satisfactory results	Unsatisfactory results all types*	Still under treatment†
Early	514	50.8	35.7	15.8
Late	1197	33.7	52.5	15.5

* Clinical and serological relapse Wassermann fastness deaths

† Progress to date such as to indicate that satisfactory outcome will be obtained ultimately

group under observation steadily decreases and the proportion of satisfactory results increases accordingly Eventually after 10 years no less than 85 per cent of the adequately treated cases of latent syphilis become clinically well and serologically negative 12.5 per cent are clinically well and reagin fast and only 2.5 per cent develop serious clinical relapse These figures are to be compared with the corresponding figures of 28 14 and 23 per cent in Bruusgaard's study[13] on the eventual outcome of untreated syphilis The difference is due to treatment

A corollary of the beneficial effect of treatment in the outcome of latent syphilis is the finding that in women with latent syphilis the proportion of children born alive and healthy is increased by treatment from 17 to 65 per cent Interesting also is the observation that pregnancy seems to exert a beneficial effect on the outcome of latent syphilis In women who were pregnant at the time their syphilis was discovered or who became pregnant during treatment satisfactory treatment results were obtained in 42 per cent. and reagin fastness or serological relapse

was observed in only 30 per cent In non pregnant women the corresponding figures were 30 and 52 per cent

Reagin Fastness in Latent Syphilis — The very fact that so many reagin fast patients eventually do become permanently seronegative suggests that reagin fastness is such is not of serious prognostic import Actually analysis of the end results in adequately treated cases of latent syphilis shows that the likelihood of clinical relapse is no greater in reagin fast patients than it is in those who have become seronegative under treatment Indeed it is entirely probable that a large proportion of those apparently rendered seronegative by treatment would be found to retain small quantities of reagin if a more sensitive test were used This has been observed repeatedly in clinics, when a more sensitive test is introduced into the laboratory Many patients previously considered seronegative then develop persistently positive serum tests Such reagin fastness in a truly latent case of syphilis has no serious prognostic significance

Suggested Outline of Treatment for Latent Syphilis — A suggested outline of treatment for latent syphilis is summarized in Table XXIV The

TABLE XXIV

SUGGESTED OUTLINE OF TREATMENT FOR LATENT SYPHILIS

1 Complete and thorough physical examination

2 Routine test of spinal fluid before starting treatment or as soon thereafter as possible

3 If early latency less than 4 years duration use outline of treatment for early syphilis *Treatment must be continuous!*

4 If late latency

Weeks	
1– 7	— 8 weekly doses neoarsphenamine 0 45–0 6 gm
8–17	— 8–10 weekly doses bismuth
18–25	— 8 weekly doses neoarsphenamine
26–37	— 12 weekly doses bismuth
38–45	— 8 weekly doses neoarsphenamine
46–57	— 12 weekly doses bismuth
58–69	— rest period
70–81	— 12 weekly doses bismuth
82–93	— rest period
94–105	— 12 weekly doses bismuth

experience of Cole and his coworkers suggests that the results with such a scheme may be improved upon further by the subsequent annual administration of a single course of heavy metals for 3 5 or even 10 years

Treatment of Syphilis Complicated by Pregnancy[123]

The urgency of antisyphilitic treatment during pregnancy is perhaps borne home by the simple statement amply supported by statistical data that a syphilitic woman untreated has only one chance in six of bearing a live healthy infant From 30 to 50 per cent of the pregnancies terminate in miscarriage or stillbirth 18 to 30 per cent of the babies die in infancy and 11 to 25 per cent of the living children have congenital syphilis

Since in most of the cases the woman herself has no clinically apparent syphilis the best and only method of demonstrating the disease is by the routine use of the blood Wassermann or flocculation test There is no evidence that pregnancy causes a false positive serological test in the absence of syphilitic infection On the contrary women known to have syphilis may have false negative tests during pregnancy Such cases however are relatively uncommon Were every woman tested at the very outset of pregnancy and were every woman with a confirmed positive serological test treated for syphilis congenital syphilis would become a rare disease

Biology of Syphilitic Infection in Utero in Relation to Treatment

If the mother acquires syphilis shortly before or after conception the fetus almost always is infected If the mother acquires syphilis after the sixth month it is said on what appears to be inadequate evidence that the fetus may escape intrauterine infection However it may then acquire the disease in passing through the birth canal Although the probability of intrauterine infection decreases as the years of the mother s infection pass by[124] this cannot be relied upon as a reason for omitting treatment

Available evidence indicates that the fetus is not infected until after the fifth month of pregnancy Treatment begun before that time may therefore prevent infection by destroying the organisms in the mother After that time treatment of the mother may be in effect the simultaneous treatment of an early infection in the fetus In confirmation of that thesis arsenic and bismuth have been shown to be retained in the fetal portion of the human placenta and have been demonstrated further in fetal organs blood and meconium[125]

Methods of Treatment

Since treatment during pregnancy is directed primarily at the prevention or cure of fetal syphilis, it must therefore be the most effec-

tive spirocheticidal treatment consistent with the safety of the mother Arsphenamine accordingly is the drug of choice although the reported results with neoarsphenamine apparently have been equally satisfactory[1-6] The results with mapharsen are as yet too few to warrant statistical evaluation Treatment always should be planned so that the patient receives the arsenical rather than heavy metal during the last three to four weeks of pregnancy If treatment is begun before the fifth month eight weekly arsphenamine injections 0 3 gm arsphenamine or 0 6 to 0 75 gm neoarsphenamine are followed by four to six doses of intramuscular bismuth together with iodides by mouth If treatment is begun after the sixth month of pregnancy, the arsphenamines should be given weekly until delivery In such cases six to eight weekly injections of bismuth should be given also on the same day as the arsphenamine treatments

Mild treatment reactions are no bar to continued treatment as they are of no consequence in comparison with the importance of obtaining a normal child Treatment cannot harm the fetus and except for the occasional case treatment even late in pregnancy will not precipitate delivery

After delivery the treatment of the mother s syphilis should continue Spinal puncture should be performed then not earlier to rule out neurosyphilis If the mother s infection apparently is recent she should be treated as if she were a case of early syphilis If the mother s infection is late she should be treated as already outlined for late latent syphilis If neurosyphilis it should receive appropriate therapy

The Detection of Congenital Syphilis

Five criteria are available to determine the ultimate status of an apparently healthy child of a syphilitic mother

(1) Perhaps the least reliable is the serological test on cord or fetal blood[17] A positive cord blood Wassermann or flocculation test may reflect simply the passive transfer of maternal reagin through the placenta and into the circulation of a normal fetus in which case the blood tests will become spontaneously negative within 4 to 12 weeks after which the child will be permanently seronegative and non syphilitic Conversely a syphilitic child may be seronegative at birth and only subsequently may develop either a positive blood test clinical evidence of syphilis or both The cord blood test is a reliable criterion of syphilitic infection only four times out of five[18] the 20 per cent error completely invalidates its use as the sole criterion of syphilitic infection

(2) The histological examination of the placenta[129] is even in the hands of experts no more reliable than the cord blood test In Williams series[130] the child developed congenital syphilis in 20 per cent of the cases in which the placenta was normal and in 12 per cent of those in whom the placenta was adjudged syphilitic the child was found ultimately to be normal The diagnostic significance of histological changes in the placenta has been questioned recently by Montgomery[131]

(3) Although it has been believed that syphilitic infection of the bones *can be identified positively by x ray*[132] *and that this alone justifies the insti*tution of treatment recent work suggests that this may not be altogether valid Thus bismuth stored in the long bones as the result of anti syphilitic treatment has been stated by Coffey[133] to be indistinguishable by x ray from syphilitic osteochondritis Moreover some children pre senting that picture failed to develop clinical or serological evidence of syphilis and the x ray changes also disappeared indicating that syphilis was not the cause of the x ray appearances

(4) Excellent results have been obtained in Germany by the darkfield examination of the scrapings from the wall of the umbilical vein[134] After the cord is cut a piece about 5 cm long is taken from the periph eral end The cord vein is dissected out carefully freed from blood and with a scalpel some tissue juice is scraped from the inner vein wall This is diluted a little if necessary with normal saline and examined at *once by darkfield The number of treponemes varies sometimes they are* present in the first preparation sometimes it is necessary carefully to search 10 to 20 preparations (Phillipp[134]) The examination is performed within a few minutes of birth A positive result establishes the diagnosis of congenital syphilis much sooner than is possible by the combined methods of serological tests placental histology and x ray A negative result does not rule out syphilis definitely but merely makes it necessary to await the results of the other examinations The procedure is strongly advised where the necessary apparatus is available as it may give imme diate diagnosis and save time in commencing treatment

(5) Perhaps the safest criterion of infection in the absence of a positive darkfield is the pediatric follow up This should include not only clinical supervision but repeated blood tests over a period of at least 12 months In infants seropositive at birth but who present no clinical evidence of syphilis these tests should be quantitative in order to establish whether the reagin titre is falling Although such falling titre would suggest that the positive reaction was due to the passive transfer of reagin it would not ex clude the subsequent development of clinical syphilis associated either with serological relapse or a sudden and continued increase in reagin titre

Outcome of Pregnancy in Syphilitic Mothers as Affected by Treatment

The data of McKelvey and Turner[128] summarized in Table XXV, clearly indicate that in syphilitic women treated during pregnancy only the ultimate outcome varies directly with the amount of treatment received. If the patients who had received 2 gm or more of arsphenamine are broken up into two groups according to whether or not they received heavy metal in addition, the striking fact is brought out that the addition of heavy metal reduced the proportion of syphilitic offspring from 22 per cent down to 6.5 per cent. The two drugs should therefore be used in conjunction even when treatment is begun late in pregnancy, when the arsphenamine should be given continuously. Essentially similar results have been obtained by Paley.[129]

The importance of beginning treatment early is illustrated by the data of Table XXV. As there shown, treatment, however scanty and

TABLE XXV

OUTCOME OF PREGNANCY WITH VARYING AMOUNTS OF ANTISYPHILITIC TREATMENT. NO TREATMENT PRIOR TO PREGNANCY

(McKelvey and Turner)[128]

Treatment during pregnancy	Number of pregnancies	Condition of child at birth, per cent		Ultimate status of child known, number of children	Of these, per cent	
		Living	Dead		Normal	Syphilitic
None	268	54.1	45.9	155	35.4	64.5
Arsphenamine*						
less than 1.0 gm	188	89.0	11.0	78	73.0	27.0
1.0–2.0 gm	127	90.6	9.4	94	79.8	20.2
2.0–3.0 gm	85	91.8	8.2	62	83.8	16.1
3.0–4.0 gm	33	100.0	0.0	24	87.5	12.5
4.0–6.0 gm	19	94.7	5.3	13	100.0	—
Total	650			426		

* Or the arsenical equivalent of silver arsphenamine or neoarsphenamine. It makes little difference whether results are expressed in terms of doses or of grams of arsphenamine since in our own clinic a fairly standard routine dose of 0.3 gm was adhered to; thus 1.0 gm of arsphenamine means approximately three injections of the drug.

however late it may be given, is better than none at all, but the earlier treatment is instituted the better are the chances of a living healthy baby.

Finally the data of McKelvey and Turner throw some light on the effect of treatment prior to pregnancy on the possibility of obtaining a healthy child even if treatment is not given during the pregnancy The data of Table XXVI suggest that adequate treatment of the mother prior

TABLE XXVI

THE EFFECT OF TREATMENT OF THE MOTHER BEFORE PREGNANCY NONE DURING PREGNANCY UPON THE OUTCOME OF PREGNANCY

(After McKelvey and Turner)[2]

Treatment of the mother	Number of pregnancies	Number of children living at birth	Ultimate status of child known number of children	Of these per cent	
				Normal	Syphilitic
Mercury only	3	2	1	–	100.0
Arsphenamine less than 1.0 gm with or without mercury or bismuth	13	12	7	71.4	8.5
Arsphenamine 1–2 gms with or without mercury or bismuth	11	8	7	100.0	0
Arsphenamine 2–4 gms plus mercury or bismuth	19	17	12	100.0	0
Arsphenamine more than 4.0 gms plus mercury or bismuth	29	4	18	100.0	0
Exact amount not known	7	4	1	–	100.0

to pregnancy may *protect against syphilis in the offspring* In this small series of patients a surprisingly small amount of treatment sufficed to achieve this purpose considerably less than that recommended as adequate treatment The authors conclude that although thorough treatment of maternal syphilis prior to pregnancy 4 gm of arsphenamine with appropriate heavy metal probably affords adequate protection for the child the mother should be treated nevertheless during pregnancy if the serum test is positive or if there is clinical evidence of syphilis

As to whether a syphilitic mother may nurse her infant the answer is in the affirmative if the mother has received six or more injections of arsphenamine during and up to the end of pregnancy This assumes that *if her own infection is recent she continues treatment* as soon as possible after delivery In cases of late syphilis the continued treatment of the mother although advisable is not essential to prevent infection of the nursing child A suggested outline of treatment of a pregnant syphilitic woman is indicated in Table XXVII

TABLE XXVII

SUGGESTED OUTLINE OF TREATMENT OF THE PREGNANT SYPHILITIC WOMAN

(Assuming that the mother's infection has been detected at about the fourth month of pregnancy)

Week	Treatment		Remarks
	Arsphenamine	Bismuth	
1	0.3		No necessity for precaution in starting with small doses. Attack! Use arsphenamine in preference to other arsenicals. If neoarsphenamine must be used make dosage 0.6–0.75 gm., not less. *Watch scleræ for jaundice and urine and blood pressure for impending toxemia.* Treatment of this intensity will not cause abortion or miscarriage. Plan length of bismuth course (6–10 doses) so that treatment ends with a course of arsphenamine just before delivery. If treatment is started early in pregnancy, alternate arsphenamine and bismuth. If it is started as late as the 7th month combine the two, a weekly injection of each given on the same day, for at least 6 doses of bismuth. Always provide an arsphenamine phase of treatment just before delivery. If treatment is started as late as the 7th month give arsphenamine weekly till delivery (10–14 doses) plus at least 6 doses of bismuth. If treatment is started as late as the 9th–10th month, give arsphenamine plus bismuth every 4–5 days. *Try to give at least 10 doses (3.0 gm.) of arsphenamine during pregnancy.*
2	0.3		
3	0.3		
4	0.3		
5	0.3		
6	0.3		
7	0.3		
8	0.3		
9		0.2	
10		0.2	
11		0.2	
12		0.2	
13		0.2	
14		0.2	
15	0.3		
16	0.3		
17	0.3		
18	0.3		
19	0.3		
20	0.3		
21	0.3		
22			
	0.3		
During puerperium	(1) Examine baby: cord Wassermann, placental histology, x-ray. (2) Test mother's spinal fluid as routine.		
After puerperium	(1) Follow baby with repeated Wassermanns for at least 6 months, better 2 years. (2) Resume treatment for mother according to stage of her infection, i.e., early, latent, neurosyphilis, etc. See outlines in appropriate sections.		

THE TREATMENT OF BENIGN LATE SYPHILIS[136]

The late inflammatory and often gummatous lesions of bones, muscles, skin and mucous membranes, which here are grouped arbitrarily as benign late syphilis, in themselves constitute a simple therapeutic problem. In about 25 per cent. of the cases, however, benign lesions are associated with more serious cardiovascular, neurological or visceral involvement

Such cases must be managed in the light of the more serious condition and do not come within the province of the following discussion

Approximately 90 per cent of the cases with benign late lesions have not had antecedent treatment and only 2 per cent have received even 12 injections of arsphenamine[136] Benign late syphilis therefore is preventable by the adequate treatment of early syphilis

Therapeutic Response

Aside from the usual drug reactions the only complication of treatment in this group is the therapeutic shock Jarisch Herxheimer reaction This is unimportant except for (a) gumma of the larynx in which case it is so dangerous that treatment must be instituted with care and (b) in osseous syphilis in which an acute exacerbation of pain for 12 to 24 hours may be followed by complete symptomatic relief If the whole bone structure is involved symptoms may not disappear completely for days or weeks

Skin lesions heal in less than 6 to 8 weeks and leave ineradicable scars The initial pigmentation gradually fades over a period of years

TABLE XXVIII

RELAPSE OR PROGRESSION IN BENIGN LATE SYPHILIS ITS RELATION TO AMOUNT OF TREATMENT

Amount of treatment (arsphenamine and heavy metal)	Total patients	Number of patients in whom progression or relapse was	
		Present	Absent
1 course or less	40	17 (42.5%)	23
2–3 courses	74	9 (1[illegible])	65
4 courses or more	81	6 (7.4[illegible])	75

No x ray improvement can be demonstrated in proliferative bone lesions in destructive bone lesions on the other hand treatment is followed by the deposition of new bone in the affected area

Serological Response and Ultimate Clinical Outcome

More than two thirds of the patients in this group are reagin fast remaining seropositive no matter how much treatment is administered As in latent syphilis such reagin fastness is of no prognostic significance

TABLE XXVII

SUGGESTED OUTLINE OF TREATMENT OF THE PREGNANT SYPHILITIC WOMAN
(Assuming that the mother s infection has been detected at about the fourth month of pregnancy)

Week	Treatment		Remarks
	Arsphenamine	Bismuth	
1	0 3		No necessity for precaution in starting with
2	0 3		small doses Attack! Use arsphenamine in pref
3	0 3		erence to other arsenicals If neoarsphenamine
4	0 3		must be used make dosage 0 6–0 75 gm not less.
5	0 3		*Watch sclera for jaundice and urine and blood pres*
6	0 3		*sure for impending toxemia*
7	0 3		Treatment of this intensity will not cause abor
8	0 3		tion or miscarriage
9		0 2	Plan length of bismuth course (6–10 doses) so
10		0 2	that treatment ends with a course of arsphenamine
11		0 2	just before delivery
12		0 2	If treatment is started early in pregnancy alternate
13		0 2	arsphenamine and bismuth If it is started as late as
14		0 2	the 7th month combine the two a weekly injection of
			each given on the same day for at least 6 doses of bis-
15	0 3		muth
16	0 3		Always provide an arsphenamine phase of treat
17	0 3		ment just before delivery
18	0 3		If treatment is started as late as the 7th month
19	0 3		give arsphenamine weekly till delivery (10–14
20	0 3		doses) plus at least 6 doses of bismuth
21	0 3		If treatment is started as late as the 9th–10th
22			month give arsphenamine plus bismuth every 4–5
	0 3		days
			Try to give at least 10 doses (3 0 gm) of arsphenamine during pregnancy
During puerperium	(1) Examine baby cord Wassermann placental histology x ray (2) Test mother s spinal fluid as routine		
After puerperium	(1) Follow baby with repeated Wassermanns for at least 6 months better 2 years (2) Resume treatment for mother according to stage of her infection i e early latent neurosyphilis etc See outlines in appropriate sections		

THE TREATMENT OF BENIGN LATE SYPHILIS[146]

The late inflammatory and often gummatous lesions of bones muscles skin and mucous membranes which here are grouped arbitrarily as benign late syphilis in themselves constitute a simple therapeutic problem In about 25 per cent of the cases however benign lesions are associated with more serious cardiovascular neurological or visceral involvement

24 injections of arsphenamine and 50 of bismuth over a period of 2 years about 10 per cent will relapse For maximum protection there should be at least 7 courses each of an arsphenamine and a heavy metal A suggested outline of treatment is given in Table XXIX

When the persistently seropositive patient is placed on probation check serological tests whether Wassermann or flocculation are meaningless unless they are quantitative In such cases a significant and persistent increase in titre beyond the limits of laboratory error may reflect redissemination and may necessitate resumption of treatment This is however uncommon If the spinal puncture originally is negative it need not be repeated

The Treatment of Cardiovascular Syphilis[137, 138]

It is important to differentiate no less than five types of cardiovascular syphilis In the first and apparently largest group the pathological involvement of the supravalvular aortic wall is so slight as to cause neither symptoms nor physical signs Although such pathological evidence of cardiovascular syphilis has been found at autopsy in no less than 70 to 90 per cent of all patients with late syphilis[138] in only 10 per cent of syphilitic individuals is the involvement sufficiently extensive to be clinically demonstrable

The most common clinical syndrome is that of uncomplicated aortitis with or without diffuse dilatation This is missed so often that it may be worth while to list in the order of relative importance seven diagnostic criteria (1) teleroentgenographic and fluoroscopic evidence of aortic dilatation (2) increased retromanubrial dullness (3) a history of circulatory embarrassment (4) a tympanitic bell like accentuation of the second aortic sound (5) progressive cardiac failure (6) substernal pain and (7) paroxysmal dyspnea In a patient with late syphilis and without mitral disease the presence of any three of these criteria strongly suggests uncomplicated syphilitic aortitis

In a third group of patients a localized destruction of elastic fibres in the aortic wall usually in the ascending portion of the aorta results in saccular dilatation or aneurysm Fourth the lesion may extend downwards to involve the aortic valves with resultant aortic insufficiency Finally in a small group of cases there may be syphilitic involvement of the myocardial wall However this is almost never observed as an isolated complication Recently Pincoffs and Love[139] have described syphilitic stenosis of the coronary ostia as a not uncommon lesion and have described a characteristic diagnostic syndrome

and does not affect the ultimate outcome Just as many patients relapse in the seronegative as in the reagin fast group As in the case of latent syphilis also the proportion of patients who do proceed to clinical progression or relapse is determined primarily by the amount of treatment they receive (Table XXVIII) In patients who receive one course or more of arsphenamine and heavy metal the probability of subsequent clinical evidence of syphilis (42 per cent) is six times greater than it is in patients who receive four courses or more These results may require

TABLE XXIX
SUGGESTED OUTLINE OF TREATMENT FOR UNCOMPLICATED BENIGN LATE SYPHILIS

Weeks	Drugs	Remarks
1–7	8 doses neoarsphenamine 0 45–0 6 gm	Test spinal fluid before starting treatment or as soon as possible thereafter If positive modify this plan
8–15	8 doses bismuth salicylate 0 2 gm	Neoarsphenamine appears to be as satisfactory as any other arsphenamine product
16–23	8 doses neoarsphenamine	Use potassium iodide for first 4 months and during bismuth courses thereafter
24–33	10 doses bismuth	
34–41	8 doses neoarsphenamine	
4–51	10 doses bismuth	Test blood Wassermann from time to time but disregard serological progress Do not stop if Wassermann becomes negative
52–59	8 doses neoarsphenamine	
60–69	10 doses bismuth	
70–75	6 doses neoarsphenamine	
76–85	10 doses bismuth	
86–91	6 doses neoarsphenamine	
9 –101	10 doses bismuth	
102–107	6 doses neoarsphenamine	
108–117	10 doses bismuth	
Thereafter	None unless necessitated by clinical progression or relapse	Test Wassermann (quantitative titre) every 6 months Periodic physical examination every 12–24 months

some modification as the patients remain under observation but the trend is unmistakable

It is of interest that in patients with benign late syphilis the tendency to relapse or progression apparently is much greater than in the analogous case of latent syphilis Moreover when relapse does occur it tends to be of the same clinical type[136]

Optimum Amount of Treatment

Because these patients do tend to relapse they require on the average more treatment than a corresponding patient with latent syphilis With

digitalized Some patients with cardiovascular syphilis especially Negroes are refractory to digitalis and relatively huge doses may prove necessary Specific treatment in such cases should not be begun until some measure of cardiac reserve has been reestablished and treatment at first is limited to the iodides and small doses of intramuscular bismuth

In undertaking the specific treatment of cardiovascular syphilis the cardinal principle to keep in mind is that the scheme of treatment must not do the patient any harm (1) The arsphenamines in general and old arsphenamine in particular used in full doses may produce a syncopal reaction culminating in circulatory failure and death within a few minutes Thus may be due to ventricular fibrillation and may be avoided largely by using the less toxic neoarsphenamine silver arsphenamine bismarsen or mapharsen in smaller doses and in more concentrated solution than ordinarily are employed (2) Even the mild treatment reactions are to be avoided A few hours of nausea and the attendant *vomiting unimportant to an otherwise healthy individual may prove a* severe strain in a patient with low cardiac reserve Here also small doses of the less toxic arsenicals serve to minimize reactions (3) The Jarisch Herxheimer reaction therapeutic shock coming on within a few hours after treatment as a local flare up of a syphilitic process may prove fatal *if the lesion is at the mouth of a coronary artery or in the wall of an* aneurysm It is avoided by beginning treatment with bismuth mercury and iodides 8 to 12 weeks before the arsphenamine in order to effect an initial slow healing of the inflammatory process and its replacement with connective tissue Even then the arsenical must be begun in small dosage e g 0 05 to 0 1 gm of neoarsphenamine (4) The therapeutic paradox [144] is said to consist of the development of congestive heart failure some time after the beginning of treatment after a period of symptomatic improvement It is thought to be caused probably by the too rapid healing of a syphilitic inflammatory process with the laying down of contractile scar tissue The patient thus may be better from a pathological point of view but much worse functionally

Suggested Outline of Treatment

A suggested outline of treatment for uncomplicated syphilitic aortitis is given in Table XXX As there shown following the preparatory course of heavy metal either arsphenamine neoarsphenamine or mapharsen preferably one of the latter two is begun in small dosage and gradually increased to the maximum dose (arsphenamine 0 3 gm neoarsphenamine 0 6 gm mapharsen 0 06 gm) Continuous treatment is

Prophylaxis of Cardiovascular Syphilis by the Adequate Treatment of Early and Latent Syphilis

As has been found for benign late syphilis the proportion of patients with early or latent syphilis who proceed to develop cardiovascular syphilis, varies inversely with the amount of treatment they have received Thus in one series of patients studied by Moore no case of early syphilis who had received 3 courses or more of arsphenamine with intermittent heavy metal had developed cardiovascular syphilis while 9 per cent of those receiving less than this amount did develop clinically recognizable cardiovascular involvement In a second series of 2 889 cases of syphilis treated early[140] many of whom had received relatively little treatment only 30 developed cardiovascular disease In a similar group of 1 936 patients with latent syphilis only 31 developed cardio vascular disease after treatment Finally Kemp and Cochems[141] in a study of 743 patients with early syphilis found that cardiovascular syphilis developed in 27 6 per cent of those who received little or no treatment for syphilis this was reduced to 13 9 per cent by inadequate treatment and no cardiovascular syphilis was observed in 113 patients who had received adequate treatment

It seems clear that the best treatment of cardiovascular syphilis is the adequate treatment of patients who have not yet developed that complication

Aims and Principles of Treatment in Cardiovascular Syphilis

One cannot hope to cure syphilitic infection in patients with cardiac or aortic involvement nor can the damaged tissues be restored to normal Indeed the study of Hood and Mohr[14] indicates that antisyphilitic treatment does not cause any significant change in the histological appearance of syphilitic aortitis Treatment does however prevent the further progression of pathological involvement Clinically this results in symptomatic relief and in the prolongation of life

To a far greater extent than in the treatment of early syphilis the treatment of cardiovascular syphilis is a combination of general medical care and antisyphilitic treatment The type and degree of involvement having been determined the patient must be forced to restrict his physical activity even to the extent of bed rest if necessary In ambulant patients who have moderate dyspnea on exertion digitalis may be used almost indefinitely in 0 1 to 0 2 gm daily doses[143] If there is actual congestive heart failure the patient must be placed in bed and fully

TABLE XXXI

SUGGESTED OUTLINE OF TREATMENT FOR ANEURYSM OR AORTIC REGURGITATION IN THE ABSENCE OF CONGESTIVE HEART FAILURE

Weeks	Treatment	Remarks	General Medical Care
1–10	10–12 × bismuth 0 2 gm potass iodide gms 4–12	To avoid Herxheimer and therapeutic paradox	Bed rest for 3–4 weeks not essential but desirable
11–20	10 × neoarsphenamine 0 1–0 3 gm or 10 × mapharsen 0 010 to 0 040 gm	*Never use arsphenamine* Start with minute doses (0 1 gm) neoarsphenamine Do not exceed 0 3 gm and reduce this if it causes reaction or use mapharsen in dosage of 0 010 to 0 040 gm	Restrict physical activity at once and permanently
21–32	12 × bismuth 0 2 gm potass iodide gm 4–12	Symptomatic relief is more prompt in aneurysm than in aortic regurgitation where it is often slow Have patience!	Digitalis unnecessary unless heart failure present but failure often may be forestalled by administration of digitalis at first appearance of mild exertional dyspnea
33–42	10–12 × neoarsphenamine 0 1–0 3 gm or mapharsen as above	Unless outspoken clinical signs of neurosyphilis are present do not perform spinal puncture The cardiovascular situation is more serious than asymptomatic neurosyphilis	
43–54	12 × bismuth 0 2 gm potass iodide gm 4–12	Watch patient constantly for impending cardiac failure — tachycardia dyspnea edema If it occurs bed rest!	Two weeks in bed every year will do no harm and may help Avoid all possible physical stress Reduce tobacco in excessive smokers Avoid alcohol Watch the urine
55–64	10–12 × neoarsphenamine 0 1 to 0 3 gm or mapharsen as above	Disregard the blood Wassermann It is often persistently positive	
65–104	Continue as above with courses of neoarsphenamine or mapharsen alternating with courses of a heavy metal and potass iodide Rest periods are undesirable but short ones not to exceed 8 weeks may be permitted if essential Avoid all treatment reactions reduce dosage if they occur or change drugs for example bismarsen instead of neoarsphenamine mercury instead of bismuth		
Thereafter	In many patients especially if symptoms persist treatment may be continued profitably perhaps indefinitely Careful follow up — periodic physical and x ray examination Renew treatment if symptoms appear		

not be begun until compensation is restored if it cannot be restored arsenicals are to be avoided permanently In any case introductory treatment with heavy metal and iodides must last 10 to 12 weeks Thereafter minute doses of neoarsphenamine (0 05 to 0 1 gm) bismarsen

TABLE XXX

SUGGESTED OUTLINE OF TREATMENT FOR UNCOMPLICATED SYPHILITIC AORTITIS

Weeks	Treatment	Remarks	General medical care
1–12	10–12 × 0.2 gm. bismuth salicylate; potass. iodide gms. 4–12 q.d.	Preparatory; heavy metal to avoid possible Herxheimer (coronary occlusion)	Bed rest and digitalis not necessary unless cardiac failure is present. If it is or if it develops later see outline for aortic insufficiency and aneurysm
13–20	8 × arsphenamine, neoarsphenamine or mapharsen	First injection small dosage (0.1 gm. arsphenamine; 0.2–0.3 gm. neoarsphenamine). Do not exceed 0.3 gm. arsphenamine or 0.6 gm. neoarsphenamine. The optimum dosage of mapharsen in cardiovascular syphilis is not yet determined but 0.010 to 0.040 gm. is probably within a safe range	
21–32	12 × 0.2 gm. bismuth; potass. iodide	Symptomatic relief usually prompt	
33–42	8 × 0.3 gm. arsphenamine or 10 × 0.6 neoarsphenamine or 10 × 0.040 gm. mapharsen	Neoarsphenamine or mapharsen probably preferable; fewer reactions. Smaller doses may be necessary if signs of circulatory embarrassment are present	If necessary for pain use amyl nitrite, nitroglycerin or theobromine derivatives with phenobarbital
43–54	12 × bismuth; potass. iodide	Test spinal fluid now or earlier to see if complicating neurosyphilis is present. If so, consider change in therapy (tryparsamide, fever)	Watch the urine
55–64	10 × 0.6 neoarsphenamine or 10 × 0.040 gm. mapharsen	Re-examine heart at frequent intervals. Watch for progression of lesion, especially aortic insufficiency	Repeat teleroentgenogram and compare measurements of aortic width at least once a year
65–104	Disregard the blood Wassermann. It is often persistently positive. Continue as above with courses of an arsenical alternating with courses of a heavy metal and potass. iodide. Rest periods are undesirable but may be permitted if necessary, especially just after a heavy metal course		
There-after	Follow the patient for the remainder of his life with periodic physical and x-ray examinations. Renew treatment with recrudescence of symptoms or physical evidence of progress as above. In any case give an occasional course once a year or thereabouts of heavy metal followed by a course of an arsenical		

indicated. The courses are long, 10 to 12 injections each, and treatment is continued for a period of at least 2 years. The patient then should be kept under observation. An annual course of bismuth and arsphenamine may be of value.

In cases of aortic insufficiency and aneurysm (Tables XXXI and XXXII) treatment must be much less intensive. Active treatment should

cardiovascular syphilis In cases of progressive optic atrophy or dementia paralytica the use of intraspinal arsphenaminized serum tryparsamide fever or any combination of these must be considered and the risks weighed

Surgical treatment of aneurysms of the peripheral vessels[146] has been developed by Matas The wiring and electrolysis of thoracic and abdominal aneurysms occasionally has been highly successful[147]

The Prognosis of Cardiovascular Disease as Affected by Treatment

The relatively good prognosis of even untreated uncomplicated aortitis not clinically recognizable perhaps is shown best by the fact that

TABLE XXXIII

THE INCIDENCE AND PROGNOSIS OF VARIOUS TYPES OF CARDIOVASCULAR DISEASE

Clinical type of cardiovascular syphilis	Approximate percentage of patients with late syphilis affected	Prognosis in terms of probable average duration of life if	
		Untreated	Adequately treated
Uncomplicated aortitis clinically unrecognizable	0–90	Good—many years no accurate data	Excellent—life probably not shortened
Uncomplicated aortitis recognizable on basis of symptoms and signs	5–10	5–10 years	10–[illegible]0 years or better
Aortitis with saccular aneurysm	1–2	1–2 years	5–15 years
Aortitis with aortic regurgitation	2–3	2–3 years	4–15 years
Myocarditis	0 2–0 5	No accurate data	No accurate data

usually it is discovered only at autopsy in patients who have died of some wholly unrelated disease[148] The beneficial effect of treatment in prolonging life in the other four categories is definite and in some cases striking (Table XXXIII)

In somewhat greater detail the effect of treatment in decreasing both the mortality of uncomplicated aortitis as well as the likelihood of its progression to graver forms of cardiovascular involvement is summarized in Table XXXIV The symptomatic relief is even more striking being observed in one series in no less than 63 out of 75 patients The unintelligent patient may feel so much better that he will lapse after a few treatments whereupon symptoms usually will recur

As in the case of uncomplicated aortitis the great majority of patient

(0 1 gm) or mapharsen (0 01 gm) are increased gradually to a maximum of 0 3 gm 0 2 gm and 0 03 gm respectively

Old age, poor general condition or such complications as extensive cardiovascular disease may modify or permanently bar this schedule of treatment

Special Aspects of Treatment

In approximately 15 to 20 per cent of patients with cardiovascular disease there is associated involvement of the central nervous system,

TABLE XXXII

SUGGESTED OUTLINE OF TREATMENT FOR ANEURYSM AND AORTIC REGURGITATION WHEN CONGESTIVE HEART FAILURE IS PRESENT

Weeks	Treatment	General medical care
1–8	Nothing except potass iodide until compensation is regained If edema is present salyrgan 0 05–0 1 gm intravenously daily or instead mercury succinimide 0 01 gm daily intravenously or intramuscularly	Immediate bed rest 4–8 weeks Prompt digitalization Morphia when necessary Slow convalescence Graduated exercise
Thereafter	If compensation improves start with 0 1 gm bismuth salicylate every 4–5 days for 3–4 doses Then increase to 0 2 gm once a week Continue for at least 12 weeks If compensation and adequate cardiac reserve are regained follow this preparatory treatment with 0 1 gm bismarsen (intramuscular) or 0 05 gm neoarsphenamine (intravenous) Increase if tolerated to 0 2 gm bismarsen weekly or by gradual steps (0 1 0 15 0 2 0 25 0 3) to 0 3 gm neoarsphenamine weekly Thereafter as in Table XXXI Mapharsen may be used also as in Table XXXI	Permanent and constant digitalis 0 1–0 2 gm every day Restrict physical activity to absolute minimum compatible with earning a living (sedentary occupation no exercise) This is permanent
Or thereafter	If sufficient cardiac reserve is not regained to permit the patient to be ambulant without edema or moderate dyspnea avoid arsenicals entirely Continue with long courses of bismuth and potass iodide alternating with rest periods of 2–3 months or with mercury by inunction Continue as in Table XXXI	Watch for recurrences of cardiac failure If they occur immediate bed rest

most commonly tabes The proper treatment will depend on which complication is productive of the greatest discomfort incapacity and risk to life Usually this is the cardiovascular disease The plan of treatment outlined for cardiovascular disease may be supplemented if necessary by tryparsamide 1 to 3 gm which has no harmful effect in

bronchi may cause stenosis and respiratory difficulty Bronchoscopic dilatation may prove helpful in such cases

Pulmonary and mediastinal syphilis are both rarities Once the diagnosis of pulmonary syphilis has been established as against either tuberculosis fungus infection or tumor any desired form of treatment may be used In mediastinal syphilis however since the local reaction following the use of arsenicals may cause increased intrathoracic pressure and suffocation introductory treatment for several months with heavy metals and iodides is necessary

Gastric Syphilis

As shown by Stokes and Brown[154] the stomach trouble of which the syphilitic patient so often complains is caused rarely by gastric syphilis and only infrequently by any organic lesion of the gastrointestinal tract In no less than 75 per cent of these cases the apparent exciting cause is syphilis of the central nervous system

Gastric syphilis actually is rare The differential diagnosis between syphilis and carcinoma is extraordinarily difficult Although some[155] favor a therapeutic test in dubious cases immediate exploratory operation would seem to offer a better prognosis for the patient hould the gastric lesion prove to be carcinoma[156] The therapeutic test if performed should consist of weekly injections of 0 2 to 0 3 gm arsphenamine with or with out heavy metal A persistent and striking gain in weight a decrease of the anemia the ability to eat large amounts of food with less discom fort are of more significance than changes in the patient s subjective complaint [155] Under continued treatment 37 per cent of the Mayo *Clinic series of 93 cases were clinically cured and 42 per cent* greatly improved

Hepatic Syphilis

In early syphilis clinical evidence of hepatic damage is most uncom mon less than 1 in 1 000 When jaundice is observed it does not com plicate treatment and responds promptly to arsphenamine

The autopsy figures for the incidence of late hepatic syphilis vary between 1 5 per cent in McCrae s series of 3 300[157] and 0 4 per cent in a series of 8 500 autopsies at the Johns Hopkins Hospital The clinical diagnosis often is difficult For the purposes of this discussion it will suffice to distinguish between acute inflammatory gummatous involve ment and syphilitic cirrhosis

with aortic insufficiency or aneurysm experience marked symptomatic relief on treatment this relief however, may not be as prompt as in uncomplicated aortitis and usually symptoms recur shortly after treatment is discontinued The presence of congestive heart failure although of serious prognostic import, does not necessarily forecast an unsuccessful outcome

Moore Danglade and Reisinger[150] have reported that adequate treat

TABLE XXXIV

Effect of Treatment on the Outcome of Uncomplicated Syphilitic Aortitis

(Moore and Metildi)[149]

Amount of treatment	Total patients	Mortality rate all causes per cent	Incidence of development of graver forms of cardiovascular syphilis (aneurysm aortic regurgitation death from congestive heart failure) per cent
None or inadequate (less than 12 doses of an arsenical)	45	42 2	31 1
Adequate (more than 12 doses of an arsenical)	70	14 2	18 5

ment effects a fourfold increase in the life expectancy of patients with aneurysm and a twofold increase in the corresponding case of aortic insufficiency It is to be noted that these were minimum figures since most of the treated cases were then still alive and most of the untreated cases had died These figures must however be qualified insofar as approximately one third of the patients were so sick when first seen that they did not survive long enough for proper therapy to be administered[151] Similarly beneficial results of treatment have been reported by Grant and by Stratton[15]

The Treatment of Visceral Syphilis

Syphilis of the Respiratory System[152]

The danger of a local Herxheimer reaction therapeutic shock in patients with gumma of the larynx has been discussed already If treatment is begun with large doses of an arsphenamine the resultant local edema may cause laryngeal obstruction and necessitate tracheotomy Heavy metal should therefore be used first for a period of at least 8 weeks and the first dose of arsenical then administered should be small

The healing of the rare ulcerative lesions in the trachea and great

Anemias Associated with Syphilis[16]

Syphilis usually is associated with rather than the cause of anemia The mild secondary anemia occasionally seen in early syphilis responds well to routine antisyphilitic treatment Any other type of anemia should be investigated and treated as if syphilis were not also present. In cases of severe anemia heavy metals should be withheld temporarily

If syphilis is associated with pernicious anemia antisyphilitic treatment may be postponed until liver therapy has restored the blood picture to normal thereafter there is no contraindication to the routine treatment.

Syphilis and Diabetes Mellitus

Although diabetes mellitus due to syphilis is excessively rare syphilis and diabetes often are associated There is no evidence that the medical care of either disease need be modified by this coincidental association

Late Syphilis of the Kidney[163] *and Syphilis Associated with Non syphilitic Nephritis*

In general there is no evidence that either the arsphenamines or bismuth in average therapeutic doses will cause renal damage as an isolated intoxication even in an already diseased kidney Nevertheless conservatism entails caution in the antisyphilitic treatment of patients with kidney damage whether or not that kidney damage is caused by syphilis

When caused by syphilis the lipoid nephrosis of Munk[164] and the peculiar type of nephritis described by Rich[165] respond well to treatment The prognosis is however poor in syphilitic chronic interstitial nephritis or amyloid disease

Treatment should be begun with small doses of an arsphenamine preferably neoarsphenamine 0 05 to 0 1 gm given in increasing doses up to a maximum of 0 6 gm or 0 3 gm of arsphenamine While the doses are small treatment may be given every 4 to 5 days If the renal lesion is syphilitic improvement should be demonstrable in 2 months If the patient does improve soluble bismuth salts then may be given intramuscularly but not concurrently with arsphenamine Insoluble preparations should not be used unless all evidences of renal damage disappear

If the urinary abnormalities disappear under treatment this should be continued as in other forms of late syphilis for 15 to 24 months If

(a) The prognosis of *acute inflammatory (gummatous) hepatitis* whether nodular or diffuse depends primarily on the extent of the hepatic damage Thus of 10 patients with ascites indicative of extensive involvement 7 died and only 1 was greatly helped by treatment On the other hand of 18 patients without ascites 12 were living and well at the time of observation and only 4 had died

Much has been said of the danger of giving arsphenamine to patients with late hepatitis because of the danger of initiating the so called therapeutic paradox[158] the too rapid healing of a diffuse hepatitis with resultant cirrhosis Accordingly in patients with ascites it may be wise to withhold the arsphenamines and restrict treatment to the heavy metals and iodides In patients without ascites however neoarsphenamine or mapharsen may be used with safety provided only that they are preceded by 10 to 16 weeks of bismuth or mercury together with iodides Thereafter small amounts of arsenical are given gradually increasing up to a maximum of 0 6 gm neoarsphenamine or 0 06 gm mapharsen Continuous treatment with alternating courses of bismuth and arsenical should be given for two years

Not only is this course of treatment without danger but in the study, already cited of the 13 patients with excellent clinical results 11 had received varying amounts of an arsphenamine averaging 20 injections

(b) *Syphilitic Cirrhosis* —A small group of patients present a clinical condition resembling atrophic (Laennec s) cirrhosis of the liver presumably as the end result of an unrecognized gummatous infiltration In the hands of Goodman and Moore[159] treatment in such patients was of little avail Chapman Snell and Rowntree[160] however report rather good results in a series of 23 cases In any event treatment with heavy metals and iodides never with arsphenamines should be tried for a period of 3 months and then abandoned if there is no symptomatic improvement

Rectal Syphilis

It has become evident that stricture of the rectum formerly thought to be diagnostic of syphilis actually is due only rarely to this cause and is instead due either to gonorrheal or tuberculous pelvic inflammatory disease ulcerative colitis trauma granuloma inguinale or lymphopathia venerea[161] Results with antisyphilitic treatment in such cases invariably are disappointing and relief depends on surgical procedures Needless to say however if a patient with rectal stricture also has syphilis he should receive antisyphilitic treatment

Clinical relapse in inadequately treated cases of early syphilis frequently takes the form of *iritis or optic neuritis occurring either alone* or as part of a neurorecurrence However such ocular involvements are due not to the arsphenamines but to their inadequate use They are cured by more arsphenamine

Treatment of Iritis Uveitis and Keratoiritis of Early and Late Syphilis

Because of the frequency with which uveitis is associated with other *clinical manifestations of syphilis either systemic or ophthalmological*[168] no patient should be treated for syphilitic uveitis until he has had a complete general and special ophthalmological examination An associated

TABLE XXXV

THE ULTIMATE OUTCOME OF THE EYE LESION IN SYPHILITIC IRITIS
(Moore and Cieske)

Type of iritis	Total patients with known outcome	Per cent of patients with vision in affected eye			
		Blind	Poor (less than useful vision)	Fair (moderate visual impairment one or both eyes)	Good (practically no residual damage)
Early	89	–	10.1	2.2	87.6
Relapsing	22	9.0	13.6	–	77.2
Late	79	1 6	15	7.6	58

cardiovascular or neurological involvement or some other and more serious ocular lesion may be the major treatment problem

The local treatment consists of the instillation of 1 per cent atropine three times daily in order to prevent adhesions between the iris and the lens posterior synechiæ If these have formed already and do not yield to conjunctival instillation the sub conjunctival injection of atropine and cocaine may cause them to break up In extreme cases the adhesions may be so complete as to cause secondary glaucoma due to lack of communication between the anterior and posterior chambers Operative interference then must be considered Although uncommon in early syphilis this occurs in about 10 to 15 per cent of patients with late iritis Dark glasses are used to protect the eyes against light and bed rest may be advisable The oral administration of sodium salicylate up to 7 gm daily not only promotes healing but acts as an analgesic

The specific treatment of iritis in either early or relapsing secondary

there is no improvement, or if the kidney involvement seems to be progressive it may be advisable to abandon treatment entirely

In cases of syphilis complicated by non syphilitic kidney involvement the decision as to the type and amount of treatment, or whether to treat at all rests on the severity of the kidney involvement and its prognosis relative to that of the syphilitic infection In patients with acute glomerular nephritis treatment should be withheld until the acute process subsides

THE TREATMENT OF OCULAR SYPHILIS[176]

The proper treatment of ocular syphilis requires the cooperative efforts of the syphilologist and the ophthalmologist Neither alone is competent to deal with both the systemic disease and its local complication The treatment of chancre of the conjunctiva gummatous episcleritis gumma of the orbit, neuroretinitis or optic neuritis offers no special problems Their treatment differs in no particular from that of the corresponding stage early or late, of systemic infection Five other ocular complications however, do call for special management (1) involvement of the uveal tract early or late (2) chronic relapsing chorioretinitis (3) optic atrophy (4) interstitial keratitis of congenital syphilis and (5) ocular operations in patients with syphilis

Effect of Arsphenamine on the Normal or Diseased Eye

Contrary to widespread impression the arsphenamines and arsenicals generally have no direct harmful action on the normal eye The only toxic effect on the normal eye is a transitory conjunctival hyperemia either associated with the nitritoid crisis or occurring as an isolated phenomenon similar in etiology to fixed dermatitis Very rarely in post arsphenamine exfoliative dermatitis there may be a superficial keratitis or a corneal ulcer The retina and optic nerve are never damaged by the arsphenamines

In the diseased eye however treatment may cause a Herxheimer reaction either as an intensification of an existing process or as a flare up of a quiescent or even unsuspected lesion Only in cases of optic neuritis is it necessary to take precautions against this Herxheimer effect[157] by beginning with small doses of arsenical e g 0 1 gm arsphenamine 0 3 gm neoarsphenamine rapidly increasing up to the average dose In all other ocular complications the Herxheimer reaction is of no practical significance and treatment need be neither curtailed nor introduced with heavy metal

Clinical relapse in inadequately treated cases of early syphilis frequently takes the form of iritis or optic neuritis occurring either alone or as part of a neurorecurrence However such ocular involvements are due not to the arsphenamines but to their inadequate use They are cured by more arsphenamine

Treatment of Iritis Uveitis and Kerato iritis of Early and Late Syphilis

Because of the frequency with which uveitis is associated with other clinical manifestations of syphilis either systemic or ophthalmological[163] no patient should be treated for syphilitic uveitis until he has had a complete general and special ophthalmological examination An associated

TABLE XXXV

THE ULTIMATE OUTCOME OF THE EYE LESION IN SYPHILITIC IRITIS

(Moore and Gieske)

Type of iritis	Total patients with known outcome	Per cent of patients with vision in affected eye			
		Blind	Poor (less than useful vision)	Fair (moderate visual impairment one or both eyes)	Good (practically no residual damage)
Early	89	–	10 1	2 2	87 6
Relapsing	22	9 0	13 6	–	77 2
Late	79	12 6	21 5	7 6	58 2

cardiovascular or neurological involvement or some other and more serious ocular lesion may be the major treatment problem

The local treatment consists of the instillation of 1 per cent atropine three times daily in order to prevent adhesions between the iris and the lens posterior synechiæ If these have formed already and do not yield to conjunctival instillation the sub conjunctival injection of atropine and cocaine may cause them to break up In extreme cases the adhesions may be so complete as to cause secondary glaucoma due to lack of communication between the anterior and posterior chambers Operative interference then must be considered Although uncommon in early syphilis this occurs in about 10 to 15 per cent of patients with late iritis Dark glasses are used to protect the eyes against light and bed rest may be advisable The oral administration of sodium salicylate up to 7 gm daily not only promotes healing but acts as an analgesic

The specific treatment of iritis in either early or relapsing secondary

diagnosis and the prompt institution of adequate treatment are essential for favorable results

Wide experience has shown that the routine treatment with the arsphenamines intravenously combined with heavy metals and iodides is of little or no value in the treatment of optic atrophy. The possible reasons for that failure will be discussed in a later section. It has been believed hitherto that tryparsamide should never be used for the treatment of optic atrophy because of its toxicity for the optic nerve. Mayer[168] however believes that its danger in such cases has been exaggerated.

Two methods are available of almost equal utility. One is the subdural treatment with *arsphenaminized serum* (for technic of preparation and administration see a later section). This may be given intracisternally, following which the patient should lie flat on his face for 3 to 4 hours in order to place the serum in intimate contact with the diseased areas around the optic chiasm. Vranesic[167] has suggested that this may be achieved also after intraspinal administration if after treatment the patient is laid across a bed with his thighs and legs on the bed, his hips at the edge and his weight supported by his crossed arms on pillows on the floor. After 15 to 20 minutes in this position he is put to bed for 10 to 15 hours with the foot of the bed elevated 12 to 18 inches.

Approximately 5 c c of serum is introduced at the first treatment and this is increased gradually at succeeding treatments up to a maximum of 15 c c. Before each injection 5 c c more spinal fluid should be removed than the volume of serum to be introduced. Treatments should be given no oftener than every 2 weeks and there should be no more than 6 consecutive treatments. These courses are alternated with courses of heavy metal. Treatment should continue for at least 4 months after there has been clinical arrest or until it is apparent that the visual failure is progressive. Some form of treatment for the systemic infection must continue. In a series of 138 patients collected by Moore from his own clinic and from the literature subdural treatment caused either improvement or clinical arrest in 54 per cent. In about 10 per cent of the patients the vision is extinguished suddenly in the course of the subdural treatment[169].

The alternative method of treating optic atrophy is with *fever therapy*. Methods of producing fever are outlined farther on in this chapter. The most important and the most valuable is malaria. Fever therapy is the method of choice when the optic atrophy is associated with paresis and taboparesis since subdural treatment is of little value in those conditions and the fever may be beneficial both for the atrophy and for the other neurological involvement as well. In 89 patients collected from the

syphilis is the same as the treatment of any other form of early syphilis. It is essential that treatment be continued in these cases for a full year after the Wassermann reaction has become permanently negative. The treatment of iritis occurring as a late manifestation is less intense and is essentially that already outlined for late syphilis, provided that there is no complicating cardiovascular or neurological involvement.

The results of treatment summarized in Table XXXV indicate that the danger of permanent visual damage is greatest in the late iritides, less in recurrent syphilis, and least in early syphilis. The permanent impairment may be due either to an exudate on the anterior surface of the lens, cataract, keratitis (with residual corneal opacities), neuroretinitis, chorioretinitis or secondary glaucoma. In late iritis many of the poor results may be attributed directly to the delay in diagnosing the ocular involvement as due to syphilis.

Treatment of Chronic Relapsing Chorioretinitis or Neuroretinitis

In this complication, fortunately rare, there are frequent ocular relapses involving the choroid, retina or the optic nerve occurring in the midst of treatment. Usually the relapse appears while the patient is on heavy metal, clears promptly with arsphenamine only to reappear during the course of heavy metal. Treatment should be modified so as to lengthen the courses of arsphenamine, 12 to 20 weekly injections. A new arsenical may be tried, and fever may be used in conjunction with chemotherapy.

Treatment of Optic Atrophy

Secondary syphilitic optic atrophy is the result of neuroretinitis, optic neuritis or extensive choroiditis and retinitis. Once it has developed, it is not significantly affected by treatment. Primary atrophy, on the other hand, is associated with central nervous system syphilis and especially with tabes dorsalis. The rate of progress is variable, the time from onset to complete blindness ranging from a few weeks to many years, but averaging 2 to 3 years. It is clear that treatment cannot restore nerve fibres already completely degenerated. The most that can be hoped for is the cessation of the syphilitic involvement at a time when sufficient fibres remain intact for useful vision. On the average, if the vision in the better eye is 20/60 or better at the time treatment is begun, there is a 50 per cent chance that the patient will retain useful vision; if it is 10/200 or less, blindness is almost inevitable. Clearly early

TABLE XXXVI

Suggested Outline of Management for Syphilitic Primary Optic Atrophy

	Method of treatment	
	Subdural	*Fever*
Indications	1 Any form of primary optic atrophy except that associated with paresis or tabo paresis 2 To follow fever therapy in patients in whom visual failure progresses in spite of fever	In optic atrophy associated with paresis or tabo paresis
Method of choice	1 In all cases except those associated with cardiovascular syphilis homologous arsphenaminized serum 2 With associated cardiovascular syphilis heterologous arsphenaminized serum (Neoarsphenamine)	Malaria
Prognosis	Even chance of arrest of vision in better eye is 20/40 or more	About 40 per cent chance of arrest of vision in better eye is 20/40 or more

Course	Weeks	Suggested treatment	Course	Weeks	Suggested treatment
I	1 3 5 7 9 11 (6 treatments) 2 4 6 8 10 12	Neoarsphenamine (0.6–0.45 gm) or silver arsphenamine (0.3 gm) followed same or next day by 6–15 cc arsphenaminized serum subdurally Neoarsphenamine or silver arsphenamine intravenously No subdural treatment	I	1–6	Malaria
			II	7–12	Tonic course of neoarsphenamine (6 × 0.3–0.6 gm)
II	13–20	8 × bismuth 0.2 gm intramuscularly weekly potass iodide grs 12 daily	III	13–20	8 × bismuth potass iodide
III	21–32	Repeat Course I	IV	21–30	30 × silver arsphenamine 0.3 gm
IV	33–44	12 × bismuth 0.2 potass. iodide			
V and after		1 If visual failure progresses try fever If visual failure is arrested for 3–4 months continue alternating courses of intravenous and intramuscular therapy for at least 2 years 3 Even if patient becomes completely blind continue treatment for sake of other possible damage from neurosyphilis Tryparsamide possible now but not before	V and after		1 If arrest of visual failure continue courses intravenously and intramuscularly for at least 2 year 2 If visual failure progresses try subdural treatment 3 No tryparsamide unless patient becomes completely blind

Control of treatment Ophthalmological survey every 3 months *Cerebrospinal fluid* every 6 months

literature fever therapy caused clinical improvement or arrest in 39 per cent However among the patients treated with malaria at the Johns Hopkins Hospital permanent arrest was obtained in no less than 85 per cent and in patients treated while the atrophy still was unilateral involvement of the normal eye was prevented in 70 per cent of the cases As in the case of subdural treatment with arsphenaminized serum in some patients vision is extinguished suddenly after a few paroxysms

Whether subdural injection or fever therapy is used the visual acuity and visual fields of patients with primary optic atrophy should be checked carefully before treatment at least every 3 months during treatment and repeatedly after treatment is ended The indications for both types of treatment and suggested outlines for the management of the patient are summarized in Table XXXVI

Treatment of Interstitial Keratitis

Interstitial keratitis is by far the most common clinical complication of late congenital syphilis Characteristically in untreated patients both eyes always are involved eventually Except for atropine and dionine dark glasses and rest local treatment is useless

Early diagnosis and treatment play a major part in a successful outcome All too often the condition remains undiagnosed for years by which time it may be irremediable Routine treatment consists of alternating doses of an arsphenamine and bismuth The arsphenamine should be used in large doses 0 1 gm arsphenamine per 25 pounds in association with 3 to 7 gms of potassium iodide daily Soluble mercury salts such as the succinimide 0 01 gm may be given daily for 15 to 20 injections skipping only the day of the arsphenamine injection Herxheimer flareups may be ignored Healing of the inflammatory reaction is a slow process and usually requires 6 to 16 weeks There are often residual corneal opacities which may slowly resolve in the following months

If this routine treatment fails to cause improvement changing the drugs used e g from neoarsphenamine to silver arsphenamine and intensifying the treatment may be beneficial Injections may be given twice weekly and bismuth used concurrently In any event treatment should be continued for at least 2 years

As shown by Carvill and Derby[10] not only are the end results in terms of visual acuity greatly improved by treatment but the incidence of relapse is decreased thereby from 27 to 3 6 per cent In 18 cases in which only one eye had been involved treatment prevented the otherwise inevitable bilateral involvement in every case but one In contrast

relatively few patients later develop clinical evidence of neurosyphilis The proportion affected is much less in females than in males and in Negroes than in whites No less than 40 per cent of previously untreated white males with late syphilis have clinical evidence of neurosyphilis as contrasted with a corresponding figure of 7 per cent for Negro females The factors other than race and sex which determine whether a given *patient with untreated syphilis will develop neurosyphilis are largely un*known The possibility of a neurotropic strain of treponemes with a predilection for the central nervous system has been discussed already By and large about 25 per cent of syphilitic patients untreated with arsphenamines will develop clinical neurosyphilis

Modern methods of treatment have affected very significantly the incidence of clinical neurosyphilis Although precise data are not available as yet it is nevertheless clear that the inadequate treatment of early syphilis less than 12 doses of arsphenamine or heavy metal increases the incidence of *early meningeal neurosyphilis* at least tenfold The approximate figures are 0 3 per cent in an untreated group as compared with 2 to 3 per cent in a group inadequately treated On the other hand with the continuous treatment of early syphilis for at least 8 months 20 injections of arsphenamine plus heavy metal this type of involvement practically disappears

Diffuse meningovascular syphilis in which there is both meningeal and vascular involvement and which includes brain gumma syphilitic epilepsy diffuse cerebrospinal syphilis and late asymptomatic neurosyphilis develops in 10 to 15 per cent of patients with late untreated syphilis Even a little treatment in the early infection suffices to decrease this probability materially and after the adequate treatment of early syphilis this complication is almost eliminated appearing in less than 1 to 2 per cent of the cases

The average incidence of *paresis* 5 to 6 per cent and of *tabes* 3 to 5 per cent is relatively unaffected by the inadequate treatment of early syphilis They are not unknown even after the adequate treatment of early syphilis occurring in 1 to 3 per cent of patients well treated by the routine methods

In summary the adequate treatment of early syphilis minimizes the incidence of late neurosyphilitic involvement Even inadequate treatment may be of benefit with respect to the incidence of meningovascular syphilis it does however predispose to early syphilitic meningitis There is now a considerable body of evidence also that treatment especially if inadequate shortens the interval between the time of infection and the appearance of late neurosyphilis[17]

with these striking results Zimmermann[167] feels that in children under 14 with only one eye affected treatment does not regularly prevent the second eye from becoming involved

Excellent results have been reported by some German workers especially Lowenstein[11], with the x ray treatment of corneal opacities resistant to ordinary therapeutic measures His method is as follows The patient s face and hair are covered by a lead mask in which there is a circular window 4 cm in diameter for the eye About 1 5 to 2 0 Holzknecht units are given from a focal skin distance of 30 cm through 4 mm of aluminum filter employing 120 K V and 4 M A Using these factors 15 per cent skin erythema dose equals 80 to 90 r A total of four or five treatments is given at weekly intervals[6]

Antisyphilitic treatment should be used in conjunction with such treatment

Ocular Operations in Patients with Syphilis

The existence of syphilis should not bar surgical procedures on the eye In case of emergency the operation may be performed at once followed immediately by antisyphilitic treatment Where delay will cause no harm a preliminary course of treatment for 4–8 weeks is adequate safeguard against either the development of ocular lesions or their exacerbation as a result of the surgical intervention Treatment in such cases should be resumed after operation and continued for as long as either the local condition or the systemic syphilitic infection renders necessary

Not infrequently antisyphilitic treatment will cause marked clinical improvement in non syphilitic inflammatory lesions of the eye sometimes when every other form of treatment has failed The possibility of such non specific improvement must be kept in mind when an arsphenamine is given as a therapeutic test in an ocular lesion suspected of being syphilitic

The Incidence of Various Types of Neurosyphilis as Affected by Treatment and their Prophylaxis

It is essential to distinguish sharply between neuraxis invasion and involvement The central nervous system probably is invaded in almost every case of untreated syphilis within the first year after infection This is evidenced by the high incidence of spinal fluid abnormalities in early untreated syphilis and by the actual demonstration of treponemes in a few instances Despite this almost universal invasion

If the fluid is negative when tested after 6 months treatment and if the patient continues regular treatment the puncture need not be repeated until the end of the first year of probation. If however the patient's treatment is irregular and especially if there have been clinical or serological evidences of relapse the second puncture should be done between the 18th and 24th month of the infection in order to detect the neuraxis involvement as early as possible.

In late syphilis on the other hand lumbar puncture should be carried out as soon as possible after the diagnosis is made in order that treatment may be adapted intelligently to the particular case. From 10 to 15 per cent of patients with untreated late syphilis and with no clinical evidence of neurosyphilis do show spinal fluid abnormalities. The incidence of such late asymptomatic neurosyphilis is not significantly affected by the presence of some other systemic lesion cardiovascular cutaneous visceral etc. The only contraindications to such routine puncture are (a) suspected brain tumor (b) pregnancy (c) extreme age particularly in patients without *clinical evidence of neurological involvement* and (d) illnesses so severe as to render asymptomatic neurosyphilis relatively unimportant in relation to the probable course of the other disease.

In both early and late syphilis a negative spinal fluid practically guarantees that the patient will not subsequently develop serious central nervous system syphilis[174]. Only about 5 per cent of patients with early syphilis and negative fluids subsequently develop neurological involvement even in the absence of treatment and when they do the type of involvement usually is mild and controlled readily by treatment. In late syphilis less than 1 per cent of neurologically normal patients with a negative spinal fluid ever develop neurological involvement and none has been known to develop tabes or paresis. The only reservation to the favorable prognosis is the possibility of a vascular involvement due to endarteritis of a deep seated vessel.

THE THERAPEUTIC MEASURES AVAILABLE FOR THE TREATMENT OF NEUROSYPHILIS

The drugs commonly used in the treatment of systemic syphilis often are ineffective in the treatment of neurosyphilis. This is ascribed usually to the fact that the anatomical and physiological barrier[175] between the blood and spinal fluid is relatively impermeable to arsenical and bismuth compounds which pass into the central nervous system and spinal fluid only in minute concentration. Three therapeutic measures are available which are of value.

In the prophylaxis of clinical neurosyphilis the adequate treatment of early syphilis is clearly of primary importance Even in cases with late syphilis but without neurological involvement routine adequate treatment can do much to decrease the possibility of subsequent neuraxis involvement This coupled with the fact that so many syphilitic patients with neurosyphilis are clinically latent only emphasizes the importance of routine blood tests on every medical patient and on the contacts of those known to be infected

Corollary to this point is the relatively high incidence of neuraxis involvement in the marital partners of those with clinical neurosyphilis[1,3] This necessitates a careful physical and neurological examination of the husband or wife of a neurosyphilitic patient Lumbar puncture should be performed either as a routine procedure or on the slightest indication of neurological abnormality a negative blood Wassermann to the contrary notwithstanding

The Diagnostic and Prophylactic Importance of Lumbar Puncture

Second in importance only to the routine adequate treatment of syphilis early or late in the prevention of clinical neurosyphilis is the routine performance of lumbar puncture in every case of syphilis Spinal fluid abnormalities antedate clinical evidence of neurological involvement by many years, and the appropriate modification of treatment in such cases of asymptomatic neurosyphilis almost always will prevent the later development of serious neurological involvement Consequently it is of the very greatest importance to recognize just as early as is possible the presence of spinal fluid abnormalities

In early syphilis under regular treatment the fluid may be tested after the second course of arsphenamine at about the sixth month of treatment Nothing is gained and harm may be done, by performing lumbar puncture in a case of early syphilis before treatment is given The spinal fluid changes which may be found in 24 to 35 per cent of the cases of early syphilis usually disappear promptly and permanently under routine treatment and are of no prognostic significance Moreover treponemes may be introduced into the spinal fluid by the puncture itself In patients with early syphilis a persistently positive Wassermann or flocculation test of the blood after 6 months of continuous treatment strongly suggests that the spinal fluid may be abnormal Conversely the more abnormal the fluid the greater the probability that the serological blood tests will not reverse under treatment

it depends on the sterile meningitis set up by the injection and lasting for 24 to 48 hours or whether the meningeal reaction increases the permeability of the blood spinal fluid membrane and thus permits the entrance of drugs or protective antibodies otherwise excluded

The method here described is that recommended by Fordyce[17] The addition of more arsphenamine or neoarsphenamine to the serum[78] or *the injection of an arsenical dissolved in spinal fluid is to be discouraged* as either procedure may cause serious reactions

The Technic of Preparation and Administration of Arsphenaminized Serum —*The patient is given an intravenous injection of 0 6 to 0 75* gm neoarsphenamine If there is a contraindication to the intravenous injection of this dose of neoarsphenamine e g cardiovascular syphilis the drug may be given to another patient his blood withdrawn and the heterologous serum administered to the neurosyphilitic patient If this procedure is adopted the patient chosen as a donor should have late rather than early syphilis to avoid the possibility of inoculating the recipient with additional treponemes Neoarsphenamine is chosen rather than any of the other arsphenamines because it is said to be removed from the circulation less rapidly From 10 to 30 minutes after the injection 30 to 50 c c of blood are removed into a sterile centrifuge tube which is allowed to stand over night in the icebox for separation of the clot This amount of blood withdrawn at this interval contains less than 0 5 mgm of the drug The next day under sterile precautions the tube is centrifuged the supernatant serum poured into a fresh sterile tube recentrifuged to remove all blood cells and transferred to a third tube The serum then is inactivated for 45 minutes at 56° C The inactivation not only destroys complement but also kills any bacteria except spore bearers which may have been introduced The serum now is ready for administration

A lumbar or cisternal puncture is performed with the patient in the lateral recumbent position in bed As soon as the dura is perforated a sterile graduated cylinder fitted with an adapter and 10 to 12 inches of rubber tubing including a glass window is attached to the puncture needle and 10 to 15 c c of spinal fluid is syphoned off by means of holding the cylinder well below the level of the puncture wound Unless the flow of fluid is free the procedure must be interrupted and another puncture made If puncture results in a bloody tap treatment should be postponed for a week The 10 to 15 c c of spinal fluid is decanted into three sterile tubes for testing While the cylinder is held at the level of the needle the desired dose of serum warmed to body temperature is poured into it first flaming the edge of the tube in which the serum is

Tryparsamide

The properties of tryparsamide its relatively low toxicity its inefficiency in the treatment of systemic syphilis and its remarkable if unexplained therapeutic activity in certain forms of neurosyphilis have been mentioned already Because of its toxicity for the optic nerve tryparsamide is considered by most observers to be contraindicated if there is evidence of optic nerve involvement nor should it be used where maximum treponemicidal activity is necessary as in early meningeal neurosyphilis

In paresis tryparsamide is the ideal follow up treatment after fever therapy which should be tried first In other forms of neurosyphilis it is advisable to begin treatment with the arsphenamines and heavy metals If there is no clinical or serological improvement within 6 months tryparsamide then may be tried

The average dose is 3 grams given intravenously and the drug usually is given in courses of 12 consecutive injections Prolonged administration sometimes for years is necessary for optimum results The necessity for the control of treatment with frequent ophthalmological examinations has been stressed in a preceding section

Acetarsone

The intravenous injection of acetarsone stovarsol in weekly doses of 1 gram has been recommended[16] in cases of neurosyphilis The method is too recent to permit of final evaluation

Subdural or Intrathecal Treatment with Arsphenaminized Serum[17]

The enormous and controversial literature concerning the merits of the intraspinal administration of arsphenaminized serum originated in this country by Swift and Ellis does not fall within the compass of the present review In most large clinics it is now felt that the procedure is of value in certain types of central nervous system involvement particularly in cases of tabes dorsalis with optic atrophy or lightning pains Intraspinal treatment should not be used in cases either with marked sphincter disturbances or with paraplegia due to endarteritis Moreover because of the risks involved in this method of treatment its use should be confined to experts thoroughly familiar with the technic of its administration It is an open question whether the therapeutic activity of the procedure depends on the minute amounts of arsenic injected whether

Fever Therapy

Wagner von Jauregg[179] *first developed the fever treatment of central* nervous system syphilis After 30 years trial with various means of producing fever employing erysipelas tuberculin vaccines sodium nucleinate etc he finally in 1917 hit upon the deliberate inoculation of patients with *tertian malaria* This has proved its value the world over and has been extended to neurosyphilitic conditions other than paresis Although many other types of febrile infections have been tried none has proved as satisfactory as tertian malaria

The mechanism of its action still is obscure (1) The *T pallidum* is highly susceptible to heat in vitro[180] and several observers have reported on the prophylactic and curative effect of fever in syphilitic rabbits[181] Nevertheless the temperatures induced by malaria and found to be effective in human cases of paresis are considerably lower than the thermal death point of the organism considered in relation to the duration of the hyperpyrexia Moreover other methods of inducing hyperpyrexia (see below) apparently are inferior to malaria (2) The possibility that the protective antibodies elaborated in the course of a bout of malaria may cross react to a certain extent with *T pallidum* must be considered seriously The fact that 10 to 15 per cent of non syphilitic patients with malaria are Wassermann positive during the febrile illness[182] may be significant in this connection and suggests a close immunological relationship (3) Finally it has been suggested[183] that malaria alters the blood spinal fluid barrier *so as to permit the greater penetration into the central nervous* system of arsenicals subsequently administered

The use of *diathermy*[184] in lieu of malaria as a means of inducing fever is predicated on the assumption that the beneficial action of malaria is based solely on its febrile action Published reports as to the results obtained with the diathermy machine[185] are too conflicting and it has been in use too short a time to warrant a definitive evaluation

The same may be said of the use of the *short wave* machine[186] which utilizing waves with a frequency of six to eighty million per second will *produce a temperature of 104 to 106° F within an hour*

Foreign protein shock[187] particularly by the intravenous injection of commercial typhoid paratyphoid vaccine has been used widely as a means of inducing fever when malaria is not available or when the patient is refractory to malarial inoculation The injection may be given either daily or every other day The stock suspension containing 2 500 million killed organisms per c c is diluted with salt solution so that the initial injection is 50 000 000 organisms the dose being approximately doubled with

continued The cylinder then is lowered again below the level of the needle so as to syphon off additional spinal fluid Since spinal fluid is of lighter specific gravity than blood serum it rises to the top of the cylinder When the cylinder contains a total volume of serum and spinal fluid of 25 to 30 c c it is gradually raised above the level of the needle and the mixture allowed slowly to flow back in by gravity When the cylinder is empty the needle is withdrawn rapidly During the syphoning off of spinal fluid the patient may complain of severe headache when 25 to 30 c c has been withdrawn This will be relieved promptly as soon as the mixture flows back in The mixing of serum and fluid is calculated first to reduce somewhat the irritating properties of the serum and second by virtue of the fact that spinal fluid rises above the serum in the cylinder to push the serum to a higher level in the dural canal than the lumbar sac where it might otherwise remain

As soon as the injection is completed and a sterile dressing placed over the puncture wound, the patient is instructed to lie on his face in order to minimize leakage through the puncture wound in the dura He is to maintain this position as long as he is comfortable and at least for 2 to 3 hours The foot of the bed is elevated 12 to 18 inches for a period of 4 to 12 hours to promote the flow of the heavier serum away from the lumbar sac cerebralwards (Vranesic Sachs Wilkins and Sams) Liquid diet is ordered for 24 hours and for the relief of discomfort morphia 10 mgm is given as a routine two hours after treatment and thereafter as necessary not oftener than every 4 hours

Subdural treatment should be given always in a hospital rather than in office or patient s home and a minimum of hospital stay of 24 to 48 hours should be demanded The physician inexperienced in the method should never attempt it his patients in whom it is indicated should be referred to the expert[6]

At least two weeks should be allowed between treatments and no more than six should be given consecutively The intracisternal route is the method of choice for optic atrophy or for lightning pains in the upper trunk the intraspinal route should be used for cases of ataxia or lightning pains in the legs

The complications of subdural treatment consist in the injection of a fibre of the cauda equina This may result in severe leg pains 2 to 3 hours later often associated with headache nausea and vomiting and lasting for 24 to 36 hours Occasionally the local irritation caused by the injection may result in transverse myelitis and paraplegia This may be of only temporary duration but occasionally the patient is permanently paralysed and bedridden

and should find wide application in Negroes approximately half of whom are refractory to tertian malaria Early reports [5] on results obtained with quartan malaria indicate that the initial results are excellent The use of ape malaria (*P knowlesi*) has been suggested also[196]

The patient to patient transfer by injecting blood carries no danger of super infection with syphilis as treponemes are not present in the blood of patients with late neurosyphilis It is therefore unnecessary to inoculate by the bite of infected mosquitos[197] or with emulsions of their salivary glands[198] Such quasi natural infections are said to be less readily cured by quinine and more susceptible to relapse than the infection caused by direct inoculation with human blood Recently however there are several reports[199] to the effect that the mosquito inoculated disease is milder permitting a larger number of paroxysms with correspondingly more favorable results

Technic of Inoculation — The blood of a malarial patient is infectious no matter when withdrawn but the incubation period may be shortened to less than a day if it is taken just before the paroxysm when merozoites are free in the circulating blood It is of interest that in the course of many patient to patient passages over a period of years the sexual form of the parasites gradually disappears Such completely asexualized strains cannot develop in the mosquito and screening of the bed therefore becomes unnecessary

If the donor and recipient are in the same or adjoining rooms one to 5 c c of blood may be taken up into a syringe from the donor the needle exchanged for a fresh sterile needle and the blood injected immediately into the recipient Otherwise the blood is drawn into a syringe containing sterile sodium citrate in the proportion 10 c c of blood to 1 c c of 2 5 per cent citrate Such citrated blood remains infectious at icebox room or body temperature for 12 to 48 hours particularly if it is withdrawn at the height of or immediately after a paroxysm when young resistant forms of the parasite predominate The blood usually is injected intravenously although other routes of administration intradermal subcutaneous intramuscular have been used also The incubation period decreases in the order named and is least with the intravenous

Susceptibility — The febrile reaction begins with a variable incubation period averaging between 3 and 8 days with extremes of 1 to 20 days If there is no take within 10 days adrenaline injected intramuscularly or a small dose of typhoid organisms 50 to 100 million organisms may have a provocative effect In about 7 per cent of previously uninfected white people the first inoculation does not take a second intravenous injection with a large inoculum 10 to 100 c c of

each succeeding injection (50 100 200 400 and 800 million) Thereafter it is increased by 400 000 000 with each succeeding injection up to as high as 3 billion organisms The injection is followed within 30 to 120 minutes by a characteristically sharp shaking chill which lasts 15 to 20 minutes during which the temperature will rise to 104° to 106° F according to the dose injected After about 1 hour the temperature gradually falls to normal over an 8 to 10 hour period

The use of typhoid H (flagellar) antigen in clear solution has been recommended[188] because the febrile reaction is said to be more constant and prolonged than after the whole suspension, and because the patient s constitutional reaction is less violent

Although pyrexia induced with *S duttoni*[189] (relapsing fever) and *S morsus muris*[190] (rat bite fever) has been used therapeutically also the results have been poor compared to those obtained with malaria The same is true of the hot bath treatment tried by several workers[191]

The Therapeutic Use of Malaria

The results obtained with malaria in the treatment of paresis and taboparesis are so much better than with any other form of treatment that when the general condition of the patient permits it should be the first form of therapy tried In other forms of neurosyphilis it should be given only if a year s previous treatment, first with arsphenamine and heavy metals then with tryparsamide has resulted in neither clinical nor serologic improvement The recent studies of O Leary[19] show that excellent clinical results may be expected with malaria in a large proportion of cases of neurosyphilis other than paresis, resistant to the routine methods of treatment Other authors[193] also have stressed the beneficial results of malaria in other forms of neurosyphilis Its use in the treatment of optic atrophy has been previously discussed in this chapter Its use is contraindicated in patients with active pulmonary tuberculosis advanced nephritis cardiac decompensation or aortic aneurysm Aortitis and even aortic insufficiency do not necessarily contraindicate its use

The benign tertian malaria transmitted from patient to patient is the strain used commonly Under no circumstances should the tropical æstivo autumnal strain be employed When for lack of a patient inoculated with a proved tertian malaria a donor with natural malaria must be used as the source of infection, the greatest care must be taken to identify *P vivax* in the blood smear and to exclude the presence of other parasites Quartan malaria has been used in patients immune to tertian[1 4]

observed is of no great moment as appetite and weight are restored promptly when the fever is terminated Long[201] reports a death rate of 3 35 per cent in 1 012 patients treated with induced tertian or quartan malaria In the 17 cases with autopsy death was attributable to acute malaria in 8 and to rupture of the spleen in 2

Termination of the Malaria — Induced tertian malaria unlike the naturally occurring disease may be completely cured with 1 to 3 gm of quinine It is unknown whether this is due to the fact that the asexual form of the parasite predominates or to the fact that treatment is given before the disease becomes chronic The drug is given 3 times daily in doses of 0 3 gm and is continued for two weeks Since the induced affection usually is quotidian there is almost always one more paroxysm *after treatment is begun* The use of atebrin and plasmochin instead of quinine has been reviewed by Craig[20]

When the condition of the patient becomes alarming but the necessity for completing the malaria is urgent 2 to 3 doses of 0 1 to 0 15 gm quinine given at 2 hour intervals during the stage of defervescence[203] will cause either (1) a temporary cessation of attacks lasting for 2 to 10 days (2) a gradual decrease in the frequency and severity of paroxysms with eventual disappearance (3) a continuation of mild paroxysms until these are stopped permanently by quinine The patient then may be re inoculated after a period of recuperation provided that no more than 3 months have elapsed since the first infection After that time he will have become refractory to malaria and will remain so for a period of years

Not infrequently malarial infection may abort prematurely before the patient has had a sufficient number of paroxysms In such cases the intramuscular injection of adrenaline the intravenous injection of 50 to 200 million typhoid organisms or even a cold bath may cause a return of the attacks Videla[204] has recommended the intravenous injection of 10 c c of 10 per cent calcium chloride for 1 to 3 days If reactivation is unsuccessful quinine should be given to prevent relapse and some other form of fever therapy e g typhoid vaccine should be tried then

Convalescence from Malaria — Four to 5 days after the fever has subsided the patient begins a course of neoarsphenamine 0 3 to 0 6 gm *given every 5 to 7 days for its general tonic and anti malarial action* The patient should remain in bed for 7 to 10 days after the last paroxysm Thereafter he is allowed up for gradually increasing periods reaching full activity in 2 to 3 weeks Ten units of insulin given twice daily 30 minutes before meals may stimulate a sluggish appetite Usually within 2 to 3 months the patient is 10 to 30 pounds heavier than he was before

matched blood to avoid a transfusion reaction is almost always successful in such instances[100]

In patients who have had malaria previously either natural or acquired there is an effective immunity developing within 3 months after the first infection and lasting for as long as 5 years Curiously enough although there is no natural immunity among whites about half of Negroes cannot be inoculated successfully with tertian malaria regardless of previous infection This racial immunity does not extend to the quartan strain

Course of Fever — The initial low grade fever observed after the incubation period lasts for 2 or 3 days after which there is a sharp rise in temperature associated with a sharp chill This lasts for 1 to 3 hours and is followed by a gradual fall to normal temperature during which there is profuse sweating Thereafter paroxysms occur at irregular intervals usually quotidian and almost never purely tertian From eight to twelve paroxysms usually are permitted counting only temperatures over 103° F and paying no attention to the number of chills

Medical Care and Complications — The temperature should be taken every 2 hours while the patient is awake and every ½ hour during a paroxysm If the temperature exceeds 106° F it may be reduced with a tepid sponge if it falls alarmingly the patient may be transfused

Malaise and headache may be controlled with codeine (32 mgm) and acetylsalicylic acid (0 3 gm) given by mouth no oftener than every 4 hours

The blood pressure should be taken twice daily If the systolic level tends to fall ephedrine 25 to 50 mgm, may be given by mouth 4 times daily and powdered digitalis (0 1 gm) twice daily If the systolic pressure falls below 70 or if there is a marked tachycardia exceeding 120 during an afebrile period the malaria should be terminated

Nothing need be done for the anemia which is observed often unless the hemoglobin falls below 50 (7 to 8 gm hemoglobin per 100 cc blood) as recovery is prompt after the termination of the malaria Mild jaundice may be ignored also The one complication, which is to be dreaded as regularly and immediately fatal is rupture of the spleen which fortunately is rare occurring in less than 0 1 per cent of the cases

Kidney function usually is only slightly impaired The blood non protein nitrogen should be taken every 4 days and the malaria terminated if it exceeds 60 to 80 mgm per cent Albuminuria and cylindruria are common and are of no significance In patients with cord bladder acute retention is common and necessitates catheterization with the attendant risk of ascending urinary infection The marked loss of weight often

thesis that the therapeutic action of malaria does not rest on the treponemicidal effect of fever alone Clinical results will be discussed in *following sections*

THE TREATMENT OF THE VARIOUS CLINICAL TYPES OF NEUROSYPHILIS

Asymptomatic Neurosyphilis '

One may classify the clinically asymptomatic patients with spinal fluid abnormalities discovered only on lumbar puncture into three groups Group I which includes those with an increased cell count with or without a concomitant increase in globulin but with negative Wassermann or flocculation tests Group III in which the changes globulin cells colloidal curves Wassermann and other serological tests are maximal and which are designated as the paretic type of fluid and an intermediate Group II

In general the prognosis of these patients varies directly with the degree and kind of the spinal fluid changes This is clearly shown in Table XXXVIII In a similar study by Moore and Hopkins[208] no less

TABLE XXXVIII

THE EFFECT OF CEREBROSPINAL FLUID ABNORMALITIES (ASYMPTOMATIC NEUROSYPHILIS) ON THE ULTIMATE OUTCOME IN EARLY SYPHILIS
(Data of Cooperative Clinical Group) [5]

Cerebrospinal fluid results	Total cases	Per cent with satisfactory outcome
Cerebrospinal fluid not tested	71	44 6
Negative	25	64 7
Group Ia Cell count 6 or over all other findings negative	69	57 3
Group Ib Cell count 6 or over excess protein Wassermann and colloidal test negative	98	56 7
Group II Cells and protein normal or slightly increased Wasserman weakly positive colloidal test negative or weakly positive	145	27 6
Group III Paretic formula	3	0 0

than 73 per cent of patients with Group III fluids already had developed clinical evidence of neurosyphilis at the time of the study and 39 per cent of those had developed either tabes or general paresis As will be shown in a following section these might all have been prevented by appropriate modifications of the treatment regime immediately on discovery of the spinal fluid abnormalities

the malaria The medical care of induced malaria is summarized in Table XXXVII

TABLE XXXVII

SUGGESTED OUTLINE OF MEDICAL AND NURSING CARE BEFORE DURING AND AFTER MALARIA

A During incubation period
1 Watch for immediate short rise in temperature if blood is unmatched
2 Patient may carry out usual activities or if in hospital need not be in bed
3 Take temperature (mouth) every 4 hours while awake
4 As soon as temperature reaches 101° F complete bed rest

B During malaria
1 Throughout course take temperature (rectal) and pulse every 2 hours while awake at start of each paroxysm and until temperature begins to fall take it every 30 minutes
2 For temperature over 106 F repeated tepid sponges Take blood pressure twice daily
3 For discomfort (headache lightning pains etc) give codeine 32 mgm and acetylsalicylic acid 0 3 gm as necessary not oftener than every 4 hours
4 To maintain body chlorides lost by profuse sweating and to prevent the resulting prostration give sodium chloride 2 gm thrice daily
5 Examine urine every 3 days
6 Do hemoglobin estimation and erythrocyte count every 3–5 days
7 Estimate blood nonprotein nitrogen every 4–5 days
8 Diet as desired Urge the patient to eat between paroxysms.
9 Support falling blood pressure with ephedrine and digitalis
10 Interrupt malaria temporarily or permanently for
a Systolic blood pressures below 70 (cardiac collapse)
b Persistent marked tachycardia in afebrile periods (pulse 120–140)
c Intractable nausea and vomiting
d Rapid exhaustion
e Rising non protein nitrogen (above 60–80 mgm per 100 c.c.)

C To end malaria
1 Give quinine sulphate 0 3 gm by mouth three times a day for 2 weeks.

D During convalescence
1 Continue complete bed rest for 7–10 days after date of last fever
2 About 4–5 days after last fever start intravenous neoarsphenamine 0 3–0 6 gm Give 6 doses at 5–7 day intervals largely for tonic effect
3 If necessary use insulin 10 units twice daily before meals to stimulate appetite
4 Resumption of full physical activity should be gradual over a period of 3–4 weeks

Pathological Changes Induced by Malaria[205] — Treponemes disappear from the brains of malaria treated paretics The inflammatory exudate in the meninges and about the blood vessels is organized and resorbed Finally there is evidence of stimulation of the phagocytic cells The fact that systemic syphilitic involvement as in the heart and liver is un affected by malarial treatment is a cogent reason for the antisyphilitic treatment of patients following malaria and is additional evidence for the

The Treatment of Early Meningeal Neurosyphilis and Neurorecurrence

Because of the necessity of attaining the maximum treponemicidal effect in these conditions arsphenamine is the drug of choice It should be given in large doses *beginning with 0 4 gm every 4 to 5 days and* increasing to 0 6 gm Potassium iodide should be given perorally at the same time 6 to 10 gm daily and in very sick patients 0 01 gm mercury succinimide may be injected intravenously daily The intensified form of treatment described on a previous page then should be continued Therapeutic results usually are apparent within a few days

The end results of treatment are highly favorable[20] They are

TABLE XXXIX

THE ULTIMATE PROGNOSIS IN ASYMPTOMATIC NEUROSYPHILIS (EARLY OR LATE)

Type of spinal fluid abnormality	Type of treatment	Approximate per cent of patients ultimately developing		
		Clinical and serological cure	Parenchymatous neurosyphilis (tabes and paresis)	Meningovascular neurosyphilis
Moderate (Group II)	Adequate Inadequate	90–100 10– 5	1–2 5–10	3–5 65–85
Intense (Group III — the paretic formula)	Adequate Inadequate	60–80 5–10	10–30 [illegible]0–80	5–10 10–20

particularly favorable when considered in relation to the grave prognosis of early meningeal syphilis if untreated or treated inadequately Thus contrasting with the 60 to 90 per cent of clinical and serological cure under adequate treatment no less than approximately 65 per cent of patients treated inadequately or not at all subsequently develop either tabes paresis or meningovascular neurosyphilis [10]

If the spinal fluid is not entirely normal within 12 months tryparsamide should be given for 6 months and if that proves unsuccessful malaria may be tried Neither malaria nor tryparsamide should be given at the outset of treatment when maximum treponemicidal effect is desired

Treatment should continue until the blood or spinal fluid become and remain negative for a full year failing such serological reversal treatment should continue for at least 2½ to 3 years *including the course of* malaria

The optimum time for the performance of the puncture in early or late syphilis and the prognostic significance of a negative spinal fluid have been discussed previously

The Treatment of Asymptomatic Neurosyphilis —The optimum treatment of asymptomatic neurosyphilis varies with the spinal fluid findings In patients with Group I fluids with mild pleocytosis and a slight increase in protein routine treatment with arsenicals and heavy metal suffices to render the spinal fluid normal in practically all cases early or late Treatment should be prolonged 6 to 12 months longer than in patients with normal fluids

In patients with Group II fluids it usually suffices to give an intensified routine treatment consisting of longer courses of arsphenamine 12 to 16 injections with somewhat larger doses 0 4 to 0 5 gm at intervals of 4 to 5 days Silver arsphenamine 0 3 gm may be used also The heavy metal courses are shortened to 4 to 5 injections The spinal fluid should be reexamined after 6 months of treatment If there is definite serological improvement as measured by a reduction in the Wassermann titre treatment is continued If however the Wassermann titre remains at approximately its original level tryparsamide should be tried for long periods in alternation with the arsphenamines and heavy metals as previously outlined If the spinal fluid Wassermann titre still is resistant after 18 months of treatment as determined by repeated examinations at 6 month intervals fever therapy should be considered O Leary[19] recently has stressed the fact that fully half of the patients whose spinal fluids remain positive under routine intravenous or subdural therapy may be rendered seronegative apparently permanently by malaria This suggests the advisability of using fever therapy in all patients of this type

In patients with Group III fluids the so-called paretic formula even intensified routine treatment is not usually productive of permanent serological reversal The prognosis of such patients is so grave that relatively drastic treatment is justified from the very outset In patients with recent infection malaria should be given after 6 months of preliminary treatment with arsphenamines and heavy metal In patients with an old infection malaria may be given at once In either case treatment should be continued after the malaria with neoarsphenamine tryparsamide and bismuth just as in paresis The minimum duration of treatment in this group should be three years

The results which are attainable in asymptomatic neurosyphilis by the treatment scheme just outlined in some detail are summarized in Table XXXIX

findings not be obtained or should it not be progressive one should try tryparsamide and malaria in that order Fever therapy is particularly indicated in patients with Group III fluids The results which may be obtained with adequate treatment as just outlined are indicated in Table XL The probability of clinical arrest and serologic negativity is

TABLE XL

The Results of Treatment in Diffuse Meningovascular Neurosyphilis

Observer	Number of cases studied	Percentage probability of excellent or good		
		clinical results	serological results	combined results
Moore Hopkins[12]	241	80	60–65	0
Stokes and Shaffer[209]	94	88	66	74.5
Fordyce[209]	139	76	43	?

doubled if the arsphenamine and heavy metal are supplemented by tryparsamide fever therapy or subdural treatment[1]

The Treatment of Auditory Nerve Involvement[13]

The auditory nerve may be involved in conjunction with any type of neurosyphilis or as an isolated phenomenon Either the cochlear or vestibular branches or both may be affected The former is far more serious as the symptoms of vestibular disturbance decrease with progressive destruction while the deafness caused by cochlear involvement is permanent

Because of the unreliability of patients impressions as to changes in hearing it is difficult to evaluate the results of treatment without the use of an audiometer One usually obtains a striking therapeutic result only if the cochlear involvement occurs in association with early meningeal neurosyphilis Half of such patients intensively treated with arsphenamine show a marked improvement in hearing In late syphilis or congenital syphilis however treatment is relatively ineffective Although the process sometimes may be halted in those with only partial involvement in others it proceeds to complete deafness despite treatment

Various workers[14] have reported fairly satisfactory results with fever therapy (malaria) Although their results have not been confirmed in other clinics it deserves further trial if only because of the otherwise hopeless outlook

Vestibular involvement is considerably more amenable to treatment

The Treatment of Vascular Neurosyphilis

The occurrence of a vascular accident in a syphilitic patient involves a nice point of diagnosis. The accident may be wholly unrelated to the syphilitic infection, due for example to cerebral arteriosclerosis and hypertension; it may be due to a focal syphilitic endarteritis with no other clinical evidence of neurosyphilis and even with a negative spinal fluid; or it may occur in association with paretic parenchymatous involvement.

Since syphilitic endarteritis is associated often with cardiovascular syphilis, such patients should not be treated immediately with arsphenamine because of the danger of a cardiac Herxheimer reaction. During a few weeks of complete bed rest bismuth may be given intramuscularly or mercury by inunction in association with large doses of potassium iodide. Neoarsphenamine should be given only after 10 to 12 weeks of this preliminary treatment and then only in small doses (0.1 gm.). It may be increased cautiously and gradually up to 0.6 to 0.75 gm. except in case of associated aortic insufficiency or aneurysm. Treatment should consist of alternating courses of an arsphenamine and heavy metal and should be carried out for at least 2 years. The prognosis is poor, and satisfactory results are obtained in only 33 per cent of patients.

When the endarteritis is associated with paresis, a far more drastic treatment is indicated, as the patient is faced with progressive parenchymatous involvement, mental deterioration and death. Malaria should be given at once and the patient treated subsequently as for paresis.

Transverse myelitis and spastic paraplegia may occur in either early or late syphilis and are due primarily to thrombosis of the spinal vessels. Arsphenamine is to be given only after a few weeks preliminary treatment with heavy metal in order to avoid therapeutic shock. Recovery depends in large measure on the reestablishment of the blood supply of the depleted areas of the cord.[11]

The Treatment of Late Diffuse Meningovascular Neurosyphilis

The highly diversified clinical picture reflects the diffuse involvement of the central nervous system. Unlike the situation in purely vascular neurosyphilis, therapeutic shock is rare and treatment may be begun with arsphenamine. Symptomatic improvement usually is prompt. The routine treatment already outlined for asymptomatic neurosyphilis is continued so long as improvement continues as determined by spinal fluid examinations at 6 month intervals. Should such improvement in the spinal fluid

Lightning Pains — Intensified routine treatment will relieve considerably the frequency and severity of attacks in about half of the patients. In the others subdural treatment may be tried. If three or four intraspinal injections at 2 weeks intervals fail to be of benefit they should be stopped and fever therapy considered. It is to be noted that even routine treatment sometimes may cause a temporary but violent exacerbation of pain.

Optic Atrophy — This has been discussed already under the heading The Treatment of Ocular Syphilis.

Cord Bladder — The urological treatment of patients with cord bladder does not fall within the province of the present discussion. Antisyphilitic treatment should be withheld until the residual urine has been decreased and the back pressure controlled by such treatment. Subdural treatment should be given only by an expert because of the danger of accentuating the cord bladder by an injury to the cord. Because of the danger of acute urinary retention fever therapy also should be used with caution and only if necessitated by other aspects of the syphilitic infection. About one third of the patients improve markedly under routine intensive treatment and appropriate urological measures.

Charcot Joints — There is reason to believe that Charcot joints reflect degeneration of the corresponding afferent nerves. Since these do not regenerate it is not surprising that antisyphilitic treatment is almost never of benefit and that patients may develop Charcot joints while under treatment. In general the treatment of these patients will be determined by the associated syphilitic complications, cardiovascular syphilis, ataxia, optic atrophy, rather than by the Charcot joints. The latter are best treated orthopedically.[16]

Gastric Crises — This, one of the most painful and distressing of all complications of syphilis, is at the same time one of the least amenable to treatment. Although acute attacks may be relieved by morphine its use should be avoided in order to prevent addiction. Codeine injected hypodermically, the rectal administration of chloral hydrate gr. 40 (2.6 gm.) and sodium bromide gr. 40 (2.6 gm.) in 30 c.c. of water, or complete anesthesia with rectal avertin may all be tried. The intraspinal injection of 1 to 2 c.c. of 25 per cent solution of magnesium sulfate has been recommended, as well as the intravenous injection of 1 to 3 mgm. of atropine sulfate repeated once or twice daily for several days.

Antisyphilitic treatment should begin with intensified routine treatment, which may lessen the frequency, duration and severity of attacks in 25 per cent of the cases. Tryparsamide may be tried then for a few months but usually it is of little help. Fever therapy is the next measure

than the cochlear physical signs are said to improve and disappear in approximately half the patients treated with arsphenamine or malaria

The Treatment of Tabes Dorsalis

About 10 per cent of tabetics fall into the category of so called burnt out tabes with little or no abnormality in the spinal fluid and with physical signs which remain unchanged over a period of years Symptomatically also they remain quiescent Treatment in such cases should be mild and prolonged consisting of alternating courses of neo arsphenamine and bismuth in moderate dosage Subdural treatment or fever therapy are not indicated In patients with active tabes however, more drastic treatment is necessary in order to prevent progression or to relieve symptoms

General Outlines of Treatment — In patients under 60 who have neither gastric crises optic atrophy nor cardiovascular syphilis one may begin with intensified routine treatment and continue as long as improvement clinical and serological is progressive If as is usually the case, symptoms or objective findings have not improved markedly after 6 months trial tryparsamide may be begun in conjunction with heavy metals These should be given for at least a year with particular precautions to avoid visual damage If serological improvement then is not evident fever therapy may be tried In all treatment should continue for at least 2½ to 3 years

Extreme age poor physical status or the presence of associated cardiovascular syphilis necessitates much less intensive treatment Neoarsphenamine or mapharsen should be used instead of arsphenamine and the interim courses of heavy metal mercury by inunction or bismuth intramuscularly should be lengthened to 3 to 4 months instead of the usual 8 weeks

Excellent or good results clinical and serological are obtained in approximately half the patients The degree of correlation between clinical and serological results will be discussed in a following section

Treatment of Special Symptoms[15] — *Ataxia* — Standard treatment relieves ataxia in only 20 per cent of the cases This is increased to about 30 per cent by the use of subdural treatment with arsphenaminized serum and recent reports indicate that 50 to 70 per cent of the patients may improve after malaria Even though there may be no improvement intensive treatment may arrest the progress of the degeneration Re education although prolonged difficult and often discouraging may accomplish much in patients seriously handicapped by their ataxia

personality change becomes evident There seems to be a definite correlation between the gain in weight and the probability of psychiatric improvement

The final outcome of malaria treatment depends on many factors one of the most important of which is the duration of symptoms which is in turn an index of the degree of parenchymatous degeneration In general the prognosis is more favorable in patients with manic and expansive psychoses the depressive dementing and paranoid psychoses are next in the order named galloping paresis has the least favorable prognosis

The end results[18] are expressed primarily in terms of psychiatric improvement and may be classified as

(1) Complete remission in which the patient is able to resume his usual occupation with his former efficiency This most favorable result is obtained in 25 to 35 per cent of the cases The probationary period which should be allowed to elapse before the patient is allowed to resume his work depend on the responsibility involved Where others lives are concerned e g locomotive engineers physicians there should be a full year of maintained remission on the other hand physical labor may be permitted as soon as the remission is obviously complete The family as well as business or professional associates should be warned of the possibility of a relapse This is observed in about one of every five patients with a complete remission and usually occurs between the first and fifth year of the remission In case of relapse fever therapy may be tried again with tertian malaria if possible and otherwise with quartan malaria or some other method of producing fever The prognosis for recovery is not as favorable in patients who have relapsed as it is for the original attack

(2) Incomplete remission occurs in about 25 per cent of the cases The psychiatric improvement in these cases is sufficient to enable the patient to work productively but there are nevertheless permanent residual psychiatric defects Although many patients who fall in this category do not deteriorate and remain at this subnormal level over long periods relapse is more frequent than it is in patients with complete remission

(3) In about 25 per cent of the cases there is an incomplete remission in the sense that the physical condition improves and the progress of the disease is arrested but there is little or no improvement in the mental status In a few patients there is a change in the psychiatric condition towards the paranoid hallucinatory type necessitating commitment

(4) In 15 per cent of the cases the course of the disease is apparently unaffected by the malaria and the patient proceed rapidly downhill

(5) A small percentage varying from 1 to 10 per cent according to

available and will relieve about 25 per cent more of the patients In those not helped by these procedures the only hope is operative treatment[17] paravertebral alcohol block posterior rhizotomy with or without section of the anterior roots as well section of one or both vagus nerves which usually necessitates gastroduodenostomy or gastroenterostomy or section of the antero lateral columns of the cord

The Treatment of Taboparesis

In patients with taboparesis the tabes may be ignored until a satisfactory remission has been obtained from the paresis Malaria should be given at once even in patients with cord bladder, as outlined in the following section

The Treatment of Paresis

The invariably fatal outcome of paresis and the long period of mental deterioration which precedes death justify the risks involved in its treatment Even in the case of patients in poor general condition immediate inoculation with malaria is the lesser of two evils as compared with the progressive and perhaps irreparable deterioration which may take place while the patient is being built up' Although the patient need not be told that he has paresis it is essential because of the unpredictable course of the psychiatric changes that some responsible member of his family be so informed and that control of his affairs be taken out of his hands by legal action if necessary

The malaria should be given in a hospital The choice between a general and a psychiatric hospital will be determined by the mental status of the patient In either event permission for committment should be obtained from a responsible relative to guard against emergency Within a few days after the malaria therapy a short course of neoarsphenamine 0 3 to 0 6 gm is given at 5 to 7 day intervals Immediately thereafter unless contraindicated by optic atrophy tryparsamide should be given in courses of 12 to 16 injections of 3 grams each alternating with short courses 8 to 12 injections of 0 2 gm bismuth salicylate continuing for a total of at least 30 injections of tryparsamide

Results of Malaria Treatment in Paresis — In some patients the psychiatric condition becomes much worse during the malaria in others it begins to improve during the fever Within a few weeks after the termination of the malaria the patient usually begins to gain in weight simultaneously psychiatric improvement sometimes amounting to a complete

The Treatment of Early Congenital Syphilis

Sulfarsphenamine is the drug of choice The toxic manifestations observed in adults occur only infrequently in children and it may be given intramuscularly in solutions as concentrated as 33 per cent

The administration of acetarsone (stovarsol) by mouth is too recent and the reported results too conflicting[221] to make a definitive appraisal possible at the present time It may be given in daily doses over a period of 8 to 10 weeks the individual dose gradually increasing from 5 to 20 mgm per kgm Its intravenous use in weekly doses of 0 2 to 1 gm has *been recommended also*[222]

Although bismuth salicylate may be injected intramuscularly in doses of 2 mgm per kgm it is often more convenient to give daily inunctions of 1 gm of 50 per cent (*U S P*) mercury ointment This is placed on the inner surface of the abdominal binder and allowed to remain there through the day

As in early acquired syphilis treatment is continuous The arsenical and heavy metal are given in alternating courses beginning with the arsenical To avoid therapeutic shock the first dose should be small 5 to 10 mgm per kgm gradually increasing to a maximum of 25 mgm per kgm A suggested schedule of treatment is given in Table XLI

Blood tests need be taken only at the beginning of each course of arsenical Treatment should be continued until the blood Wassermann reaction has become and remained negative for one year The minimum amount of treatment should be five courses each of sulfar phenamine and heavy metal over a period of about 18 months Since 20 to 25 per cent of syphilitic infants have asymptomatic neurosyphilis spinal puncture should be done after 6 months treatment and repeated at the end of the probationary year In the series studied by Jeans and Cooke[223] this type of treatment cured 72 per cent of the patients despite the fact that some patients received as little as 6 months treatment The presence of a positive spinal fluid had no significant effect on the amount of treatment *required* as the fluids rapidly became *negative*

The Treatment of Late Congenital Syphilis

General Observations — Cardiovascular syphilis is almost unknown in late congenital syphilis and neurosyphilis occurs in only 15 per cent of the untreated cases as contrasted with 25 per cent in late acquired syphilis The treatment of late congenital syphilis without neurological involvement and with no active lesions is essentially the same problem as

the general physical condition and associated syphilitic complications die during or after the malaria as a result of the treatment itself

The end results obtained in cases of paresis treated with tryparsamide alone apparently compare favorably with the foregoing results obtained with malaria Various workers [19] have reported essentially similar results complete or partial remission in 40 to 50 per cent of the cases All are agreed [20] that the ideal method of treatment is the combined malaria followed by the *prolonged* administration of tryparsamide

Post Treatment Management of Neurosyphilis

For the first 3 to 5 years after the cessation of treatment the patient should be checked at 6 to 12 month intervals to ensure that his condition remains stationary both symptomatically and clinically Physical examination should include a neurological examination and both blood and spinal fluid serological tests should be repeated Actually the blood findings are of little significance but the reappearance of either an increased number of cells or of a positive Wassermann reaction in a spinal fluid rendered normal by treatment justifies the resumption of treatment even in the absence of clinical evidence of progression After the fifth year the patient need be examined only at 12 to 18 month intervals In the case of paretics the family should be warned to watch for signs of relapse

The Treatment of Congenital Syphilis

Congenital syphilis differs from acquired syphilis in many important particulars The syphilitic infant has a much more profound constitutional disturbance than the patient with primary or secondary syphilis Liver spleen bone marrow kidneys and lungs are involved and the mortality of the disease if untreated is 25 to 50 per cent depending on the severity of infection and the general physical condition of the infant Despite these differences the congenitally syphilitic infant like the patient with early acquired syphilis can be cured of his infection by adequate treatment and remain permanently well and seronegative If the congenital child untreated survives the early acute stage he may after a variable latent period, develop lesions of late congenital syphilis which tend to localize particularly in the eye bones inner ear and nervous system At this time however as in the late acquired disease radical cure usually can not be accomplished The patient must be content with symptomatic relief and clinical arrest

outcome Interestingly enough unlike the analogous case of late acquired syphilis in Smith s series a relatively small amount of treatment less than 30 weeks proved just as effective as a large amount in preventing either clinical relapse or progression Similarly approximately half of the patients remained reagin fast and that proportion was unaffected by the amount of treatment received Moreover as in the analogous case of late latent acquired syphilis the progno is of the reagin fast group was just as good as in those rendered seronegative by treatment Finally and again unlike acquired syphilis there was no indication that the ultimate outcome in a group of treated cases improved with the passage of time

The Treatment of Late Latent Hereditary Syphilis

The justification for treatment in this group lies in the protection thus afforded against subsequent interstitial keratitis or nerve deafness Thus only 4 of 115 cases of late latent congenital syphilis observed by Smith subsequently developed active lesions despite the fact that many of the patients in the series were treated before the age of 11 to 15 when the lesions usually appear and were observed well beyond that critical period

The Treatment of Interstitial Keratitis

Treatment for this is already described under the heading The Treatment of Ocular Syphilis

The Treatment of Nerve Deafness

It is of interest that nerve deafness due to heredosyphilis is not associated with neurosyphilis and that the pinal fluid almost always is normal This indicates that the lesion is not in the central nervous system but perhaps in the inner ear nerve organ There is little or no possibility of restoring hearing by treatment

The Treatment of Congenital Neurosyphilis

Unlike neurosyphilis resulting from acquired syphilis neurosyphilis as a late manifestation of congenital syphilis is just as common in females as in males The prognosis of the asymptomatic form is the same as in the acquired disease This is not true of juvenile paresis which has a much worse prognosis The methods of treatment[23] are the same as those

TABLE XLI

SUGGESTED OUTLINE OF TREATMENT FOR EARLY CONGENITAL SYPHILIS

Week	Drug	Dose	Remarks
1	Sulfarsphenamine	5–10 mgm /kgm	Test blood Wassermann. Avoid therapeutic shock.
2–7	Sulfarsphenamine	25 mgm /kgm	
8–11	Mercury by inunction daily or Bismuth salicylate weekly	1 2 gm mgm /kgm	
12–19	Sulfarsphenamine	25 mgm /kgm	Test blood Wassermann. *Do not stop treatment when Wassermann becomes negative*
20–25	Mercury or bismuth		
26–33	Sulfarsphenamine	25 mgm /kgm	Test blood Wassermann. Also test spinal fluid at about this time
34–41	Mercury or bismuth		
42–49	Sulfarsphenamine	25 mgm /kgm	Test blood Wassermann. Note gradual lengthening of heavy metal course 4 6 8 and now 10 weeks
50–59	Bismuth or mercury		
60–67	Sulfarsphenamine	25 mgm /kgm	Test blood Wassermann. This is absolute minimum of treatment which should be continued longer if necessary to fulfill serological standards
68–79	Bismuth or mercury		
80–132	Probation No treatment		Test blood Wassermann every 2 months. Test cerebrospinal fluid at end of year
There after	Prolong follow up with physical and blood Wassermann reexaminations every 6–12 months until puberty is passed and if possible thereafter at least until early adult life is reached		

that of late latent syphilis Where intravenous medication is feasible neoarsphenamine may be given in adult dosage as outlined already for late latent or late benign syphilis If intramuscular injection is necessary sulfarsphenamine may be given as in infants Bismuth should be given in preference to mercury

Clinical and serological cure was effected after more than one year's treatment in only 44 per cent of the cases in the series of Jeans and Cooke[223] However the satisfactory clinical results clinical arrest over a minimum observation period of 3 years is much higher than these figures would indicate Thus Smith[224] obtained satisfactory results in 75 to 85 per cent of those with active lesions when first seen and in 80 to 95 per cent of those with late latent congenital syphilis The results were somewhat better in Negroes than in whites primarily because of the higher incidence of neurosyphilis in whites Neither sex nor the age at which treatment was begun had any demonstrable effect on the therapeutic

reflects unavoidable fluctuations in the sensitivity of the laboratory test the serum reagin content actually remaining more or less stationary

(5) Because of the widely varying sensitivity of different laboratory procedures a patient may be rendered apparently seronegative by treatment and remain seronegative for years only to become definitely and persistently positive if the serum is tested in a second laboratory or if the laboratory technic is made more sensitive Such change in reactivity clearly does not constitute a serological relapse it reflects the persistence of minute amounts of reagin in an adequately treated patient

(6) The spinal fluid reagin apparently is elaborated locally in the central nervous system itself the presence of a positive spinal fluid *Wassermann reaction is therefore pathognomonic of neurosyphilis* Taken in conjunction with the pleocytosis and the spinal fluid globulin content the change in the titre of the spinal fluid Wassermann reaction is often the only available measure of the efficacy of the therapeutic regime

(7) It is generally held[illegible] that the persistence of positive serum tests in adequately treated patients reflects the presence of residual foci of infection The possibility must however be considered seriously that such patients are biologically cured in the sense that all the organisms have been *killed* and that the *serum reagin is merely a carry over continuing* to circulate in slowly decreasing concentration over a period of years long after the infection has been completely eradicated

Reagin Fastness in Early Syphilis[illegible]

The interpretation and significance of the serological tests in cases of early syphilis under treatment has been discussed in a previous section

Most patients with early syphilis who receive continuous treatment become seronegative within 6 months Failure to reverse within that time does not necessarily imply reagin fastness as the serum reagin content already may have fallen from an initial titre of e g 200 to one of 10 Although the qualitative serum test remains positive the reagin titre in such cases is falling continuously and may continue to decrease with further treatment The majority of those who are still seropositive at that time become and remain seronegative under continued treatment within the following 6 months *Provided that the spinal fluid is negative* failure of the serum tests to reverse within 6 months is therefore of no prognostic import However spinal puncture always should be performed in such patients to rule out asymptomatic neurosyphilis Neuraxis involvement is almost twice as common and infectious relapse more than

vals thereafter for evidences of healing. The effect of treatment on the Wassermann titre should be observed also by means of quantitative tests.

The Serological Tests in Relation to Treatment

For the proper interpretation of the serological results of treatment it is important that the physician have clearly in mind certain basic aspects of the laboratory tests for syphilis[111a]

(1) There are only two serological tests for syphilis complement fixation and flocculation and the dozens of tests which have been devised and which are now in use are only modifications of those two basic technics. Moreover the same substance in syphilitic serum determines both complement fixation and flocculation

(2) The routine reports of positive doubtful and negative* offer no clue to the amount of reagin which may be present in the serum. A given serum may contain 100 or even 1 000 times the amount of reagin necessary to give a definite positive result. The reagin content may be expressed quantitatively as the titre of the serum i e as the highest dilution in which it is seropositive. To the best of our present knowledge the actual Wassermann titre at the beginning of the treatment is of neither diagnostic nor prognostic significance

(3) It follows from the fact that a serum may contain several hundred units of reagin that the persistence of a positive laboratory test over a period of months does not necessarily mean that the patient is reagin fast i e that the serum reagin content is stationary. The titre may be falling continuously over that period and it is only at the very end of the curve when reagin has almost disappeared that the routine laboratory test becomes doubtful or negative. This progressive fall becomes apparent only if the laboratory test is done quantitatively throughout the course of treatment

(4) In true reagin fastness the serum reagin titre i e the highest dilution which gives a positive Wassermann or flocculation test remains more or less stationary despite continued treatment. Such reagin fastness may be observed at either a high or low level of reagin content. In the latter case the result of repeated serum tests may vary from positive to negative to positive to doubtful. It is as yet unknown whether this is due to slight variations in the reagin content of the serum or whether it

* The old classification of 4+ 3+ 2+ and 1+ is being rapidly discarded for the reasons cited in this paragraph. Such reports do not furnish a quantitative measure of the reactivity of the serum. *Positive* includes those tests previously reported as 4+ or 3+ *doubtful* includes the 2+ and 1+ results

the conditions just discussed serological reversal is not the purpose of treatment Rather treatment is prolonged in order to prevent the development of more serious complications with the additional possibility that these already may have begun are as yet below the threshold of clinical recognition and may be arrested by adequate treatment Once the patient has received an amount of treatment which will serve this dual purpose of arrest and prevention i e a minimum of two years of continuous treatment with courses of arsphenamine and heavy metal treatment may be stopped regardless of the serum tests The patient must however be reexamined at intervals with particular reference to central nervous system syphilis Not infrequently after treatment has been discontinued the serum tests gradually fade out over a period of years and become permanently negative

Reagin fastness per se in adequately treated patients with late syphilis in general and with late latent syphilis in particular therefore has no serious prognostic significance Progression and relapse are no more common among the Wassermann fast group than they are among those whose serum tests are reversed more readily Moreover having received adequate treatment the reagin fast individual may marry and have children with as little danger to his wife and children as in the case of the patient rendered permanently seronegative *A persistently positive serum test in an adequately treated patient with no demonstrable cardiovascular visceral or central nervous system syphilis is entirely compatible with long life good health and permanent non infectiousness*

The Serological Control of Treatment in Neurosyphilis[21]

In early neurosyphilis as in early systemic syphilis the serological response to treatment is so prompt and regular that it serves as a convenient guide post to the duration of treatment

In late neurosyphilis however as in any other form of late syphilis the *blood tests* are of little or no value as a guide to treatment The serological response in the spinal fluid is however of importance The excess cells and total protein disappear so rapidly under treatment as to be of little value The criteria of interest are (1) the spinal fluid reagin content determined quantitatively by the minimum amount of fluid necessary to give a positive Wassermann test and (2) the globulin content which usually is measured in terms of colloidal precipitation rather than by actual analysis

As indicated in Table XLIII the spinal fluid readily is rendered normal even by routine intravenous treatment in most cases of early meningeal

three times is common in reagin fast cases of early syphilis as they are in those rendered seronegative by treatment (Moore and Padget [4])

Reagin Fastness in Late Syphilis

The approximate incidence of reagin fastness in various types of syphilis despite adequate treatment is indicated in Table XLII The

TABLE XLII

THE INCIDENCE OF WASSERMANN FASTNESS IN VARIOUS TYPES OF SYPHILITIC INFECTION

(Early syphilis treated for at least 6 months late syphilis for at least 1 year)

Type of syphilis		Per cent Wassermann fastness with adequate treatment
Early syphilis (primary and secondary)		5-15
Latent syphilis		35
Late cutaneous and mucosal		50
Late osseous		65
Late visceral (hepatic etc)		50-70
Late cardiovascular		50
Central nervous system	Meningeal	10-20
	Meningovascular	40-50
	Tabes	10-25
	Paresis	70-80
Early congenital		5-20
Late congenital		60-80

proportion is greatly increased under intermittent or irregular treatment Conversely half of reagin fast patients with late syphilis have central nervous system involvement about one third have cardiovascular or osseous involvement and approximately one fifth have visceral or cutaneous involvement In only 6 per cent of the cases can no lesions be demonstrated These proportions add up to well over one because in many patients more than one system is affected

It follows that every patient who proves reagin fast on treatment should be examined carefully to ascertain the possible cause of the reagin fastness Teleroentgenogram and spinal puncture are an essential part of that examination Should syphilitic involvement be demonstrated treatment proceeds as already indicated for that particular system In either cardiovascular visceral or central nervous system syphilis no attention need be paid to the blood Wassermann or flocculation tests Symptomatic relief clinical arrest and prolongation of life are the goals of treatment and not the reversal of the blood tests

In late latent cutaneous osseous and late congenital syphilis as in

justify an ex cathedra statement there is nevertheless reason to believe that as in the analogous case of reagin fast latent syphilis the prognosis of such patients is almost as good as those in whom treatment results in complete serological reversal Thus 35 of 40 well treated patients with persistently positive spinal fluid Wassermanns observed by Keidel and Moore have remained without relapse or progression over periods ranging from 2 to 20 years after the cessation of treatment In five of these the spinal fluid abnormalities disappeared spontaneously during the observation period without further treatment All four deaths and six of the seven relapses observed in the 46 patients occurred among the 29 who did not receive malaria More recently Goodman and Moore[30] have found clinical progression or relapse in 12 5 per cent of those with persistently positive spinal fluid Wassermanns as compared with 4 8 per cent in those rendered seronegative by treatment Although this represents a somewhat more definite correlation between serological tests and prognosis than obtains in the analogous case of reagin fast latent syphilis it is obvious that a persistently positive spinal fluid Wassermann is not of necessarily bad prognosis Similar results have been observed by Dattner[230]

The Provocative Wassermann

The first injection of an arsphenamine into a syphilitic patient is said often to cause a marked rise in the serum reagin content which usually reaches a maximum in 5 to 10 days In patients with a definitely positive serum Wassermann or flocculation test this provocative rise is of academic interest only However in patients in whom the serum tests are negative or conflicting and in whom the clinical findings suggest but are not diagnostic of syphilitic infection this provocative rise may be of diagnostic significance by causing the serum test to become definitely positive Blood should be drawn before the arsenical is injected (0 3 gm arsphenamine 0 6 gm neoarsphenamine) and every other day thereafter for 14 days In a successful test negative or dubious tests become and remain definitely positive for a period of at least 4 to 6 days The significance of these positive reports is materially increased if the test is done quantitatively and the result reported as a titre i e the highest dilution in which the serum is positive An increase from a titre of less than 1 doubtful result to one of 8 is clearly of diagnostic significance

Once the diagnosis of syphilis has been established in such a patient treatment must be continuous and prolonged in accordance with the

syphilis Late meningovascular syphilis also is relatively susceptible to serological reversal In tabes routine treatment is relatively ineffective in restoring the spinal fluid to normal and subdural (intrathecal) treatment tryparsamide or fever therapy usually are necessary to effect spinal fluid negativity In paresis fever therapy succeeds in 50 per cent of the cases tryparsamide reverses the spinal fluid in approximately half as many It is of interest that the serological reversal effected by malaria rarely becomes apparent in less than 18 months, and that the proportion of patients who develop negative spinal fluids as a result of malaria therapy steadily increases over a period of 5 years, finally attaining a maximum of 65 per cent

TABLE XLIII

SEROLOGICAL RESULTS (SPINAL FLUID) IN VARIOUS TYPES OF NEUROSYPHILIS

Type of neurosyphilis	Estimated percentage probability of attaining permanent spinal fluid normality by means of			
	Standard intensified treatment (arsphenamines and heavy metals)	Subdural (intrathecal) treatment	Tryparsamide	Fever therapy
Early meningeal (including asymptomatic)	80–90	80–90	80–90	80–90
Late diffuse meningovascular	50–60	50–60	60–70	70–80
Tabes	40–60	70†	60†	60–80†
Paresis	0–2	0–5	25–30	50–60

* Of these nearly a half have normal fluids before treatment
† Including only patients with abnormal fluids before treatment

There are many patients who are rendered seronegative without clinical improvement conversely many patients retain a strongly positive spinal fluid Wassermann reaction despite definite symptomatic cure and permanent clinical arrest In general the correlation between clinical and serological results is highest in meningeal and meningovascular neurosyphilis and less in tabes and paresis[1] In the latter two categories only half of those with excellent clinical results are also rendered serologically negative by treatment

We have now to consider the prognosis of those patients without clinical evidence of neurosyphilis who retain a positive spinal fluid Wassermann despite prolonged continuous and adequate treatment over a full three year period including intensified routine therapy tryparsamide and fever therapy in the order named Although the available data do not

this is certainly not the answer to the problem of the prevention of syph ilis Too many potentially infectious individuals would deliberately or carelessly omit its use and the adequate dissemination of information to the lay public undoubtedly would meet with opposition on moral grounds[30] It is nevertheless a highly effective measure for the preven tion of disease protecting men and women alike

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methods already discussed If the presenting complication in a patient known to have syphilis proves to be non syphilitic the type and amount of antisyphilitic treatment may be conditioned by the nature of the complicating disease Thus, it is obviously useless to treat for late latent syphilis a patient with an inoperable malignant tumor or advanced hepatic cirrhosis

The Prophylaxis of Syphilis

There are several effective methods available for the prevention of syphilis The local inunction of 2 to 4 grams of 33 per cent calomel ointment into the penis and scrotum preceded by thorough washing with soap and water proved remarkably effective in the American Expeditionary Force during the World War and particularly so if applied within a few hours after exposure [31] The soldiers were made thoroughly aware of the necessity for and value of this prophylactic treatment Nevertheless on their return to civil life they made no attempt to apply that knowledge in the following 20 years requests for prophylactic treatment from physicians have been conspicuous by their absence That experience indicates that but little can be expected from the establishment of prophylactic stations no matter how intensive the accompanying educational program may be The inconvenience the fear of publicity or embarrassment and the lack of compulsion all serve as effective deterrents[32]

It has been suggested that the injection of arsphenamine 24 to 48 hours after exposure may be an effective prophylactic measure Although such single large injections will effectively 'prevent i e cure syphilis in experimental animals inoculated 24 to 48 hours previously [33] results in rabbits cannot be immediately interpreted in terms of the human infection and it has not been demonstrated that such prophylactic injections do permanently abort the human disease Indeed by suppressing the early manifestations of syphilis conceivably they may cause positive harm The physician and patient may be led to believe that the disease has been prevented and the patient with a latent and unsuspected infection may proceed to develop serious late neurological or cardiovascular complications These considerations apply with equal force to the bismuth prophylaxis suggested by various workers [34] An intramuscular depot of insoluble bismuth compound if sufficiently large apparently does protect rabbits against inoculation with syphilis its value as a prophylactic measure in human beings remains to be proved

No prophylactic measure yet suggested has the general applicability and efficacy of the physical protection afforded by the condom Even

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PART II

PENICILLIN THERAPY

Introduction

In June 1943 Mahoney, Arnold and Harris[1] presented preliminary data suggesting that penicillin was effective against *Treponema pallidum* in early syphilis in rabbits and in man The mixture of substances employed by them under the name penicillin was the product of the mold *Penicillium notatum* as originally described by Fleming[2] Because of the unique circumstances associated with the national emergency it was possible to set up a nation wide, integrated campaign of study under the auspices of the Committee on Medical Research (O S R D) By October the investigation was under way in 41 clinics and in eight laboratories of experimental syphilis As a result of their collected efforts an enormous amount of factual data was compiled During the first three years approximately 35 000 patients were treated and the results (for early syphilis) reported to a central statistical unit[3] These data form the basis for most of the following discussion on penicillin in early syphilis The published reports on the more immediate effects of penicillin in the various types of late syphilis together with experiences from the Syphilis Clinic of the Johns Hopkins Hospital will be summarized as well A portion of these data has been presented in detail in monograph form[4]

Although a tremendous bulk of information has accumulated in a relatively short time it is important to bear in mind that the essentially chronic and insidious nature of the syphilitic process imposes limitations on the conclusions one is at present justified in drawing Many years must elapse before we will be able to say whether or not penicillin therapy influences the incidence and severity of the serious late sequelae of syphilitic disease such as cardiovascular and neurosyphilis Even then due to the paucity of untreated control material reported in the literature it will be possible only to compare the post penicillin results with those of patients who have received various amounts of metal chemotherapy or fever treatment in the past These considerations are of greatest importance in attempting to evaluate long term results, we are not justified at present in doing more than describing what has transpired during the brief five year period that penicillin has been available for study

ciated with the absorption delaying diluent (e g peanut or sesame oil beeswax) or to substances in chemical combination with the penicillin (e g procaine) Most are minor and self limited and do not require interruption of treatment more often than one time in 1 000 This is in marked contrast to the older methods of therapy The administration of 1 200 milligrams of mapharsen in five days by intravenous drip for example caused death in one of every [illegible]00 patients treated prolonging the time of administration of that quantity of mapharsen to 1[illegible] weeks reduced the mortality to one in [illegible]000[6] Though a very few deaths have been reported as supposedly due to penicillin administration these are unconvincing as to the direct responsibility of the drug

Brevity of Treatment —There is probably no aspect of syphilotherapy which has been modified more acutely by the advent of penicillin than the duration of treatment Whereas the duration of active metal chemotherapy was not infrequently measured in years the majority of penicillin schedules thus far studied could be completed within a brief span of days This should hold as well for the newer ambulatory schedules as it did for the various in patient treatment regimes employed during the preliminary evaluation of the antibiotic

High Proportion Completing Treatment —Approximately 999 of each 1 000 patients admitted to hospitals for the penicillin therapy of early syphilis completed the outlined course of injections This resulted from the brief period required for the entire treatment and the fact that these patients were admitted to institutions It is a common observation that as the time required for an ambulatory schedule to be administered is increased the number of patients failing to complete treatment likewise increases Enthusiasm and concern subside as a result of discomfort and inconvenience Since good results have been obtained using in-patient penicillin schedules 4 to 15 days in length it is not unreasonable to expect comparable results after ambulatory penicillin regimes of similar duration

Ease of Administration —This advantage is of prime technical importance Even newborn infants may now be given satisfactory courses of treatment using the intramuscular route which may be completed before they leave the nursery

The objection to peanut oil beeswax preparations on the grounds that completely dry syringes and needles were required has been overcome in a new aqueous suspension of procaine penicillin G with which wet sterilized equipment may be used

General Considerations

A discussion of the chemistry and pharmacological activity of penicillin does not fall within the scope of an article such as this The product originally employed in the experimental treatment of syphilis was a mixture, as we now know, of several chemically distinct penicillins and various impurities Today the species F dihydro F, G, X and K are well recognized, and most studies are carried out with one specific compound The various penicillin species were studied in experimental rabbit syphilis by several investigators, and it was found that penicillin G was the most effective and K the least so[5] As a result of these findings, as well as the obvious advisability of using a known chemical compound since July 1946 crystalline penicillin G (benzyl penicillin) has been used exclusively in the studies carried out through the Syphilis Study Section of the National Institute of Health Preliminary analyses have shown that the results in human syphilis likewise have been superior when crystalline penicillin G was used rather than the amorphous mixture

It is unreasonable to deny that penicillin is a valuable adjunct to syphilotherapy or that it is at least in some respects, superior to any previous form of treatment That it has serious limitations must be admitted by its most ardent protagonists Defining these limitations, as well as the study of as yet unsolved problems having to do with time dose relationships and the causes of treatment failure, are under investigation at the present time The material presented here should, therefore not be interpreted as final, this section is more in the nature of a progress report

Penicillin presents many advantages over the older methods of syphilotherapy but has certain disadvantages as well Since these considerations are of basic importance in all aspects of treatment, they will now be considered in detail

Advantages of Penicillin Therapy

Lack of Toxicity —Penicillin is a relatively innocuous substance The untoward reactions thus far reported to have followed its use have been confined almost exclusively to allergic manifestations in the skin These reactions may occur early or late in the course of treatment or even be of the delayed serum-sickness' type They are frequently asso

which will retain most of the advantages of penicillin treatment together with the elimination or at least modification of some of the disadvantages cited Already it has been pointed out that one major difficulty encountered in the semi intensive arsenobismuth schedules was that the time required for treatment was of necessity prolonged, such drugs were dangerous and as one compressed the time in which the required therapeutic dosage was given *the mortality rate rose sharply to a prohibitive* level Ambulatory penicillin schedules at present under study range in duration from 8 to 70 days In all of them patients who have completed the first 2 to 3 weeks of a given schedule have had amounts of penicillin G or penicillin G plus arsenic and bismuth as great or greater than are being given in the routine in patient treatment of early syphilis throughout the country Although offering great promise too few patients have been followed as yet for a sufficient period of time to permit long term statistical conclusions to be drawn Certainly however patients taking two or three weeks treatment will fail no more frequently than those treated previously with aqueous crystalline penicillin G and by prolonging the total duration of therapy for those who do come as directed, the chance for cure should equal or surpass that obtainable with arsenic and bismuth preparations It is hoped that a much shorter course will yield the same chance of cure but to a greater proportion of patients who start treatment than has been true for example of the 9 to 1 week semi intensive arsenobismuth schedule

PENICILLIN IN EARLY ACQUIRED SYPHILIS

Penicillin in Uncomplicated Early Infectious Syphilis —The goals of the treatment of early syphilis are twofold From the standpoint of the public health it is important to render the syphilitic patient noninfectious rapidly and if possible permanently From the patient s viewpoint the desired end is eradication of the disease from his body He wants to be cured of his chancre his secondary rash or other clinical manifestations plus a lasting reversal of all laboratory tests to normal If freedom from relapse and prolonged normalcy of serological and spinal fluid tests for syphilis up to five years after treatment indicate cure of early syphilis in man penicillin is curative As was pointed out in the previous section however it is by no means uniformly so and we have no way at the present time of telling in advance which patients will achieve the desired result

Disadvantages of Penicillin Therapy

Treatment Failures.—Data at present available concerning results obtained in the treatment of early acquired syphilis with amorphous penicillin have shown that the failure rate was 25 to 35 per cent. These percentages are made up of approximately one half representing infectious muco-cutaneous relapse or reinfections and one half sero relapse and sero resistance. These figures have been appreciably modified by the use of penicillin G, only 5 to 10 per cent of these patients undergo clinical infectious relapse or reinfection. No method is at present available to tell in advance which individuals will fail subsequently and require retreatment. Since one patient in 10 may be expected to fail after a single course of treatment with penicillin G, the necessity for intensive serological and clinical follow-up of all penicillin treated patients for months and years becomes obvious.

Desirability of Hospitalization.—Although hospitalization was responsible, in large part, for the high proportion of patients completing penicillin treatment, it was not without its disadvantages. The number of hospital beds available has been limited, undoubtedly numerous patients have been denied penicillin treatment for that reason. For many, on the other hand, one or two weeks in a hospital has been a hardship involving loss of income or even loss of employment. It is hoped that the ambulatory penicillin schedules now under study will satisfactorily overcome this disadvantage.

Penicillin in Non-syphilitic Diseases.—Penicillin, unlike arsenic and bismuth preparations, is employed with great frequency throughout the country for a variety of conditions. This has made it a matter of difficulty in recent years to evaluate properly the histories of these patients and to decide whether or not adequate therapy for a concurrent syphilitic infection has been given.

Expense.—The administration of aqueous penicillin on an in-patient basis is expensive when compared to the sums required to treat the same number of patients with the older arsenobismuth schedules. On the other hand, the use of the slowly absorbed penicillin G preparations, such as procaine penicillin in oil or aqueous suspension, permits brief and economic ambulatory treatment.

It is with these latter preparations that current studies are mainly concerned. Several schedules using penicillin in peanut oil beeswax and the procaine penicillin suspensions are now under investigation. This effort is directed toward the determination of a rationale of therapy

oil beeswax (POB) Within the total dosage range of 4 8 to 9 6 million units and within the time limits of daily or twice daily injections for 8 to 16 days or twice weekly injections the results appear to be as good as with the drug in aqueous solution Schedules now under investigation with penicillin G in peanut oil beeswax and procaine penicillin in oil or in aqueous suspension are expected to yield a lower failure rate than with the amorphous preparation

Although these findings may fall far below the optimistic expectations entertained by some in 1943 a simple statistical calculation will show that these figures represent results which are probably superior to those obtained with arsenobismuth treatment In the Johns Hopkins Clinic for example it has been shown that only 37 5 per cent of patients starting a 9 to 12 week semi intensive arsenobismuth schedule finish it[1] Of those who do so 96 per cent achieve cure The probability of curing 1 000 patients by this regime would be 0 96 (cure rate) times 0 375 (the number who would be eligible for cure by finishing treatment) In short 332 of the 1 000 would be cured With penicillin even although we take the least favorable rate of cure reported (e g 65 per cent) 99 per cent will complete therapy and of each 1 000 started on treatment in the hospital 643 would achieve a satisfactory result

These figures serve well to emphasize that follow up examinations should be frequent and thorough The chance for clinical relapse probably diminishes with time as the total exposure to risk of reinfection increases These cannot be separated with certainty in man and from the practical public health standpoint it does not matter since immediate retreatment is imperative in either case It is our policy to examine these patients monthly for the first year This includes a thorough examination of the skin and mucous membranes and a quantitatively titered serologic test for syphilis If all is well one year after treatment the intervals are increased to every 3 months during the second year and every 6 to 12 months thereafter We attempt to keep all such patients under permanent surveillance In case suggestive lesions appear or there is a significant rise in titer the patient is watched closely until the syphilitic nature of the process is proved or disproved When retreatment is necessary the same follow up procedure is initiated If the pretreatment spinal fluid is normal it is rechecked during the second year providing the blood serologic titer is low or has become negative If the spinal fluid is positive prior to treatment it is examined every 3 to 6 months until it has become and remained for several years normal If after penicillin treatment a previously negative spinal fluid should become positive for

The following information, representing results obtained in the nation-wide study during the first four years, is subject to modification as the investigation continues[3] It is presented here as a means of orienting the reader as to the many variables concerned and the general results obtained When amorphous penicillin was used in aqueous solution the optimum total dose, within the time limits of 4 to 15 days, was in the range of 1 2 to 2 4 million Oxford units The results were essentially equal whether this total dose was given in 4, 8 or 15 days, and whether individual injections were given at intervals of 2, 3 or 6 hours Duration of infection was shown to be a significant factor as was true with arseno-bismuth therapy, since the best results were obtained in patients with seronegative primary syphilis Here the duration of the chancre was usually of one week or less, and the total duration of infection probably averaged 3 to 6 weeks There was found to be a sharp increase in the failure rate in persons with seropositive primary syphilis with duration of lesions, 8 days to about 8 weeks, and of infection, 4 to 12 weeks, failure rates which were increased still further in those with secondary syphilis Conflicting reports have appeared concerning the results following the addition of arsenic and/or bismuth to these penicillin schedules, but most investigators feel that these drugs may add substantially to the final incidence of cure

The failure rate at 12 and 24 months after treatment with any system of amorphous penicillin administration so far tried, between the dosage ranges of 1 2 to 9 6 million units and within the time periods of 4 to 15 days was 25 to 35 per cent These failures were made up of approximately one half infectious, mucocutaneous relapse, with which were combined reinfections and one half serorelapse and seroresistance Infectious relapse and reinfection are not clinically separable with assurance in man To the extent, to which so called clinical relapses actually represent reinfection the results are better than those cited but at best the over all failure rate, excluding possible or probable reinfections, was 15 to 25 per cent

Only preliminary data are available as yet concerning the large number of patients with early syphilis treated since July, 1946 with crystalline penicillin G in aqueous solution but they suggest that the results will be significantly improved The failure rate with this drug probably will be in the neighborhood of 10 to 20 per cent or less, the infectious relapses making up approximately one half of this incidence

Preliminary information, up to 12 months after treatment is available for the absorption delaying method of amorphous penicillin in peanut

for the diagnosis implies that (1) these seropositive patients have no symptoms or signs referable to active syphilis and (2) that the cerebrospinal fluid be normal However from the standpoint of the internist and the syphilologist this group is of major theoretical and practical importance We know these patients underwent a generalized dissemination of *T pallida* during the first few days or weeks of their disease nevertheless they are at present asymptomatic On the other hand all *patients with symptomatic late syphilis except neurosyphilis were at* one time classifiable in this diagnostic category Why do some untreated patients remain latent or even become seronegative and present no recognizable syphilitic lesions at necropsy Why do others develop aneurysms gummas deafness or die of cardiac failure secondary to aortic regurgitation It is this large apparently healthy but potentially ill group that offers the greatest promise and challenge to a treponemicidal agent

Whether penicillin administered in the latent stage will prevent symptomatic late syphilis is a question that cannot be answered on the basis of a five year follow up which is the longest at present available We do know that penicillin is no more effective in overcoming seroresistance than was arsenobismuth therapy There is no indication for penicillin administration in patients with latent syphilis adequately *treated by the older methods, in an attempt solely to attain seronegativity* In untreated patients with early or late latent syphilis, 2 to 5 million units of penicillin should be as efficacious in a preventive sense as treatment with arsenic and bismuth In either case the post treatment follow up should continue at gradually increasing intervals throughout life In the event that late symptomatic syphilis be found following such abortive treatment immediate therapy should be employed directed at the particular manifestation which has appeared as outlined in subsequent sections

Penicillin in Late Acquired Syphilis

For the purposes of this discussion early syphilis becomes late *at or about the end of the second year of infection It is at this time that* mucocutaneous relapses become extremely scarce in untreated late secondary syphilis. It is at this time also that the majority of seropositive patients may be classified as seroresistant in spite of all amounts and types of treatment including penicillin It is at about this time that new neuro-

the first time, retreatment would be imperative Although these procedures may appear formidable, it is surprising as well as gratifying to see how cooperative such patients may be, when each is encouraged and helped by the physician to take an intelligent interest in his particular problem

Penicillin in Complicated Early Syphilis

Most of the complications of early syphilis such as iritis, uveitis, headache or periostitis subside promptly, i e , within 24 to 48 hours, after the administration of the first injections of penicillin It is not infrequent that these signs and symptoms become intensified for a brief period, the so called Jarisch Herxheimer reaction (therapeutic shock) These reactions have not proved to be serious in early syphilis usually producing only a transitory elevation of temperature, and they represent no contra indication to further penicillin therapy

In three sets of circumstances penicillin appears to be especially advised, acute syphilitic meningitis, early visceral syphilis and in patients with infections resistant to arsenic and bismuth In acute syphilitic meningitis the meningeal involvement may be overwhelming with the sudden onset of cranial nerve palsies, including eighth nerve deafness and vestibular dysfunction Penicillin produces, as a rule, prompt sub sidence of these symptoms and sustained improvement In patients having nephrosis associated with early syphilis it is important to impose no additional chemical insult on the injured renal parenchyma Penicil lin, as opposed to arsenic, and especially bismuth, is free of such poison ous action The same argument might be applied to the diffuse hepatitis said to be associated with florid secondary syphilis Finally, a small group of patients has been described in which the infection was peculiar in being resistant to ordinary or unusually high dosages of arsenic and bismuth Penicillin has yielded good results in this condition

To date no evidence of penicillin resistance has been seen either in patients or in the experimental laboratory, those patients, who fail after one course frequently get good results after retreatment with the same or larger amounts of the antibiotic

Penicillin in Early and Late Latent Acquired Syphilis

Latent syphilis comprises the great bulk of patients with this disease but is not of great interest from the standpoint of the medical student,

one should not hesitate to use metal chemotherapy when the clinical and pathological evidence points to this diagnosis and penicillin has failed to produce resolution The mechanism of action of penicillin probably is concerned both with destruction of *T pallida* and with the secondary bacterial invaders Local cleanliness rest of the affected part and good general medical management combined with the antibiotic therapy should enable most patients to heal these lesions completely

The visceral gummas involving such organs as the liver have been shown to respond well to penicillin in both acquired and congenital late syphilis

In one set of circumstances particular caution should be observed Two instances of edema of laryngeal gummas following the initiation of arsenical therapy were noted in this Clinic in the pre penicillin days one necessitating tracheotomy one causing death by suffocation We have had the opportunity to give penicillin to only one patient with a laryngeal gumma Although no untoward symptoms were noted in this case the Jarisch Herxheimer reaction should be borne in mind Accordingly patients presenting such lesions probably should be treated in the hospital with facilities for emergency tracheotomy immediately available

The late manifestations of syphilis of the skeletal system have been shown to respond to penicillin at least as far as the prompt relief of acute inflammatory signs and symptoms is concerned When there has been chronic bone destruction or proliferation however little objective change may be seen in serial roentgenograms Since the process apparently has been halted by the drug early diagnosis and prompt institution of treatment appear to be the means of preventing gross deformity or permanent disability in these patients The outstanding exception to these statements is the Charcot joint associated with tabes dorsalis in which penicillin appears to exert no beneficial effect

Penicillin in Cardiovascular Syphilis

The signs and symptoms of syphilitic cardiovascular disease characteristically appear 15 to 5 years after the primary infection It is probable nevertheless that the basic damage to the great vessels began during or immediately after the original treponematemia Among those patients who eventually will develop demonstrable lesions there is a long period of asymptomatic syphilitic aortitis which is difficult or

syphilis stops appearing, the patient, who has passed through the first two years of a syphilitic infection, with or without therapy, and who is then found to have a normal spinal fluid, has virtually no chance, barring reinfection or superinfection, of showing an abnormal cerebrospinal fluid on subsequent examinations[8]

Late acquired syphilis logically falls into four categories First is benign late syphilis, commonly manifested by gummas of the skin the visceral tissues or the skeletal system Treatment usually is readily efficacious and even without therapy, these manifestations seldom threaten life The next two groups of syndromes are the most serious of all cardiovascular and neurosyphilis Once symptoms of heart disease or paresis have appeared, these patients if untreated, succumb eventually to the disease, barring intercurrent disease or accident, and in other types of neurosyphilis chronic invalidism is frequent Finally we have the group of ocular manifestations which, at least in the case of untreated primary optic atrophy, end in total blindness It is obvious that the early diagnosis and treatment of these last three conditions is one of paramount importance to the internist

It is perhaps less obvious that these conditions are extremely difficult to evaluate from the therapeutic standpoint Untreated, the survival or maintenance of useful central vision in the case of optic atrophy may extend over years or even a decade or more The course of the untreated conditions for humanitarian reasons, has not been firmly established Finally except in the case of dementia paralytica, these are all conditions characterized by few, if any, demonstrable *T pallida* Not only the older metal chemotherapy but penicillin as well has been directed at one certain function destruction of treponemes It is gratifying therefore that in nearly all of these serious conditions penicillin has been reported by some to be of benefit

Penicillin in Benign Late and Visceral Syphilis

Although gummas may be disfiguring and of great concern to the patient and his family, they are seldom a threat to life and for that reason are designated benign ' These lesions may occur anywhere on the skin or mucous membranes, where they may be confused with neoplasm, tuberculosis stasis ulcers or other dermatologic disorders, but as a rule they respond promptly to a single course of penicillin in amounts of to 5 million units[9] Penicillin-resistant gummas have been reported, and

reported in the literature we are inclined to think that this risk may have been unduly emphasized

We subscribe to the feeling that the time to treat cardiovascular syphilis is during the period of early syphilis long before the metastatic vascular lesions have become clinically manifest On the other hand patients with overt cardiovascular syphilis are liable to acute surgical conditions accidents and infectious diseases The evidence at the present time suggests that penicillin should be given in full therapeutic dosages for the acute condition there is no proof that it does harm On the other hand penicillin eventually may be shown to have a beneficial effect on the cardiovascular syphilitic process but many more years of observation are required before that problem may be properly evaluated

Penicillin in Neurosyphilis

Except for early acute syphilitic meningitis the neurosyphilis associated with early acquired syphilis is asymptomatic Although from 20 to 35 per cent of patients with manifest secondary syphilis have abnormal cerebrospinal fluids the results of therapy whether with metal chemotherapy or with penicillin are effective in reverting the great majority of these promptly to normal These patients seem to have labile or responsive fluids in comparison with those from patients having neurosyphilis of more than two years standing We believe that the most effective method of reducing the incidence of late neurosyphilis is the adequate treatment of the early disease and that in this regard penicillin is probably as effective as other methods of therapy

Following penicillin administration the usual response of the neurosyphilitic process as measured by laboratory criteria is rapid and sustained improvement In general the worse the spinal fluid the greater the initial improvement The so-called group III or paretic formula type of fluid characterized by elevated cell count and total protein content a positive complement fixation reaction with concentrations of spinal fluid smaller than 0 2 c c and a first zone colloidal gold or mastic test may be improved significantly by the end of a 7 to 5 day period of treatment Characteristically the cell count falls to normal first followed shortly by the total protein content Both are usually within normal limits by 2 to 6 months after the beginning of therapy The colloidal test reflecting as it does abnormal spinal fluid protein next becomes reduced The last factor to be affected is the Wassermann reaction and as seroresistance is frequent in late syphilis treated or untreated so it

impossible to diagnose clinically Even at necropsy there may be argument between pathologists as to whether a given lesion is syphilitic or not This has resulted in large part from the use of variable criteria and on the location and number of tissue blocks taken for histological study When arteriosclerosis and hypertension further complicate the findings in the aorta and about the coronary ostia, or when rheumatic fever has deformed the valve leaflets, it may be impossible in the syphilitic patient to determine what degree of cardiovascular disease is due to syphilis The paradox lies in the fact that it is during this latent period, especially during the first year or two of the syphilitic infection, that antisyphilitic treatment might be expected to be of maximal value Penicillin, like arsenic and bismuth, can no more be expected to restore the fragmented media or distorted valvular leaflets to normal than it can be expected to replace or repair destroyed elements in the central nervous system Since there has been no unequivocal proof even that the older methods of treatment prolonged life, when administered to individuals with symptomatic cardiovascular syphilis, it would be premature at this time to attempt an evaluation of long-term results following penicillin administration

Some preliminary evidence has accumulated, however, in regard to the so called Jarisch Herxheimer reaction in cardiovascular syphilis[10] Although used originally to designate an intensification of the skin lesions in patients with early syphilis within the first 24 to 48 hours after the initiation of treatment, the term has since come to be used loosely for almost all types of conditions in which syphilitic patients become worse before they become better ' following the administration of treponemicidal drugs During the early period of massive syphilotherapy with salvarsan (606 ') it was noted that patients with cardiovascular syphilis not infrequently had severe immediate reactions, death occasionally occurred within a few minutes or hours after the first injection It became the custom to initiate treatment in such patients with long courses of bismuth on the assumption that the reaction could be attenuated Such a procedure has been recommended by some prior to the administration of penicillin There is no more evidence that this is indicated than there is that the use of small initial doses of penicillin, e g, 500 to 1000 units will modify the reaction, should it occur On the basis of our own experience and the vast numbers of patients receiving penicillin for other unrelated conditions, e g following surgery, for pneumonias, etc, together with a striking paucity of severe reactions

reported in the literature we are inclined to think that this risk may have been unduly emphasized

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seems that the reagin content of the spinal fluid may be reduced in many cases but not entirely eliminated, at least within the first 4 to 5 years after treatment

From the standpoint of judging therapeutic outcome, Dattner and Thomas[11] believe that the colloidal test and the Wassermann reaction of the spinal fluid are not of paramount import To them the continued reduction of the cell count and protein content to normal limits constitutes a successful result since they feel that this reflects a subsidence of the syphilitic process in the meningeal and parenchymal parts of the central nervous system Such fluids are designated by them as inactive Although objections may be offered to this concept particularly in tabes dorsalis and other degenerative processes in the central nervous system it is useful in evaluating those cases, in which the inflammatory element is marked These fortunately make up the bulk of the cases seen, and in them penicillin is most effective in reverting an active to an inactive cerebrosphinal fluid within a few weeks or months

Results of penicillin treatment of early acute syphilitic meningitis have been good in our experience, so far as the central nervous system disease is concerned On the other hand, these patients have been as likely as others with early syphilis to undergo reinfection or infectious relapse, and the same intensive follow-up routine should be employed

Patients with late neurosyphilis have been classified in many ways One of the most useful methods, when used together with the Dattner Thomas concept of activity, is to employ a clinical estimation of the degree of inflammatory activity present as opposed to the extent of degeneration Although most, if not all, patients with neurosyphilis have both inflammation and degeneration in the central nervous system, the laboratory and clinical differences between a patient with typical early general paresis and one with tabes dorsalis usually are marked In the former the spinal fluid is active, and there are psychiatric evidences of changes in mental status, there may be no objective evidence of neurological disease The tabetic, on the other hand, may have an inactive or even a negative cerebrospinal fluid but show evidences of profound neurological dysfunction e g, abnormal pupils absent or diminished knee and ankle jerks and signs of posterior column disease Whereas the paretic exhibits the findings suggestive of inflammatory activity, the tabetic more strongly suggests degeneration Necropsy studies confirm the clinical impression, *T pallida* usually are demonstrated with ease in the brains of paretics, but they have been found only rarely in the spinal cords of tabetics

The concepts of activity and of inflammation versus degeneration in the central nervous system may be carried one step further. Since these abnormalities presumably resulted from the presence of *T. pallida*, and since penicillin is a treponemicidal drug, such conditions might be expected to respond to penicillin therapy, provided there be mainly inflammatory activity due to these organisms. The main limiting factor might be the amount and location of degenerated or scarred nervous tissues remaining. When treponemes have done their damage, as in tabes dorsalis or in Erb's spastic paraplegia, leaving demyelinated columns and tracts in the spinal cord, treponemicidal agents, including penicillin, would be expected to be of little value. When there is no evidence of neurological disease clinically, as in asymptomatic neurosyphilis, the antibiotic might be most efficacious. Follow up periods have been too brief, however, and reports have in many cases been too conflicting to say with certainty that penicillin is entirely effective even in asymptomatic neurosyphilis. The following tabulation (Table I), modified from Penicillin in Syphilis[4], lists the various diagnostic categories of neuro-

TABLE I

TREATMENT OF CHOICE IN LATE NEUROSYPHILIS BY MAJOR DIAGNOSTIC CATEGORIES

TREATMENT OF CHOICE	DIAGNOSTIC CATEGORIES
Penicillin alone	Asymptomatic (early or late) Acute syphilitic meningitis Diffuse meningovascular neurosyphilis Gumma of brain or spinal cord Vascular neurosyphilis
Penicillin, induced fever optional	Nerve deafness due to syphilis Erb's spinal spastic paraplegia
Penicillin plus induced fever	General paresis Taboparesis Tabes dorsalis Syphilitic primary optic atrophy

syphilis and what we at present feel to be the treatment of choice for each.

Conditions listed in the second and third sections of Table I are characteristically extremely serious, constituting definite threats to life or vision Penicillin alone has been a signal failure in the majority of patients with primary optic atrophy of moderate or severe degree Results in tabes dorsalis likewise have been poor, lightning pains have responded in a few cases but Charcot joints little if at all In paresis the end result depends to a marked degree on the severity and duration of the psychosis When the changes in mental status have been present only a short time and require an experienced physician for their recognition, either malaria or penicillin therapy usually will yield good results Since either improvement or arrest of the process constitutes a therapeutic success, patients markedly psychotic prior to therapy may be treatment successes but nevertheless remain totally disabled Improvement may occur in most unexpected instances, however Since induced fever therapy has been shown to be efficacious in many of these cases particularly in paresis[1] and in optic atrophy[13], it seems to us unwise to temporize with other methods of therapy in which results have been equivocal at best, i e , penicillin alone It has been shown experimentally also that increased temperature enhances the bactericidal activity of penicillin For these reasons we feel that patients with these grave parenchymatous types of late symptomatic neurosyphilis deserve combined fever-penicillin therapy

Penicillin in the Prevention of Congenital Syphilis

There is probably no aspect of the problem of syphilis in which penicillin has been more encouraging than in the prevention of infantile congenital syphilis by treatment of the pregnant woman Results with the older methods were good, when the diagnosis of syphilis in the mother was established during the first trimester, thereafter, and increasing to term the risk of an infected child was present regardless of the type of arsenobismuth therapy administered Once the fetus had become infected from the mother, which occurs after the fourth month of pregnancy only intensive treatment carried throughout the pregnancy could yield a healthy child When the mother became infected during pregnancy there was little prospect of a non-syphilitic baby unless treatment was carried out vigorously Since the avent of penicillin this entire picture has been changed radically[14] Now it makes little difference when during a given pregnancy the diagnosis of syphilis is made or

when the mother contracts her disease, provided penicillin treatment may be completed prior to the ninth lunar month Even though the fetus be infected in utero administration of adequate amounts of penicillin to the mother will act not only against the mother s disease but also against that of the fetus as well Penicillin administration does not cause increased uterine irritability with resulting miscarriage

Reports in the literature are unanimous as regards the excellent results obtained following penicillin administration in syphilitic pregnant women The reported failure rates in the neighborhood of 2 per cent have been due largely to inadequate dosages employed in the 1943 44 period when supplies of penicillin were scanty or to failure on the part of the patient to be examined during each trimester When syphilitic mothers have been treated with more than 3 million units of penicillin and when they have not relapsed or become reinfected later in pregnancy virtually all the offspring have been normal Relapse or reinfection if promptly retreated with penicillin need not produce syphilis in the child

The effectiveness of penicillin depends upon careful serological and clinical observations performed on the mother It is our policy to perform an examination of the skin and mucous membranes and to obtain a serological test for syphilis monthly through pregnancy in penicillin treated women Should relapse or reinfection be encountered retreatment is instituted immediately Results have been excellent

We do not feel that retreatment with penicillin is necessary during each succeeding pregnancy provided the original post penicillin course has been satisfactory e g negative serological tests or falling serological titer no clinical evidence of disease We do examine these women at monthly intervals during each subsequent pregnancy however since relapses may occur two or more years after the original treatment and because reinfections may take place at any time The effort required to perform these routine examinations is small indeed if only one congenital syphilitic infection is thereby prevented

Penicillin Treatment of Congenital Syphilis

Infantile Congenital Syphilis

At the present time we believe 100 000 to 400 000 units per kilogram of body weight divided into 80 to 120 aliquot doses given at two or

three hourly intervals is adequate treatment for early congenital syphilis. If the newer slowly-absorbed preparations are used, such as penicillin G in peanut oil beeswax or procaine penicillin G in sesame oil or in water, the total gravimetric dose may be divided into 10 to 12 daily doses with the same results. The latter type of preparation is distinctly preferable to the drug given intravenously or intramuscularly in aqueous solution because of the need for only a single injection each day as compared to from 8 to 12 when aqueous solutions are so used, a difference which might be life-saving in an extremely ill baby.

The more frequent varieties of congenital syphilis encountered are early latent, as manifested by rising or sustained serological titer only, cutaneous (condylomas, erosions mucosal snuffles) and osseous (osteochondritis within the first 2 months, osteoperiostitis thereafter). As a rule, adequate penicillin treatment reverts the serological test for syphilis to negative promptly in these cases. The cutaneous or mucocutaneous lesions become dark field negative for *T. pallidum* within 12 to 24 hours and involute within a few days. The osseous lesions clear rapidly from the clinical standpoint in that bone pain and pseudoparalyses promptly vanish. The radiographic changes lag some weeks or months behind the clinical improvement. When treatment is instituted prior to the second year of life however, completely normal adult skeletal development may be anticipated. The hepatomegaly and splenomegaly as well as the generalized lymph node hyperplasia, which are seen frequently regress gradually after treatment. As in the acquired disease the abnormal cerebrospinal fluid associated with early congenital syphilis usually is found to have become entirely normal 6 to 12 months after penicillin therapy, as a rule the Wassermann reaction is the last of the laboratory findings to become normal.

Although penicillin therapy enables one to complete antisyphilitic treatment in a brief period and without the use of such cytotoxic drugs as arsenic and bismuth preparations, an apparent paradox has been noted in that the infant mortality rate, 10 to 12 per cent, in infantile congenital syphilis has not been appreciably altered. It is our opinion that such deaths depend on two factors not attributable to penicillin treatment. In the first place babies who have had in utero syphilitic disease for 4 or 5 months prior to delivery may survive the ordeal of birth but have such profound damage to vital structures that adequate post natal development is impossible. In addition, since these babies usually are born without benefit of medical care into environments characterized by slovenliness and ignorance, frequently they are malnourished, dehy-

drated and the victims of multiple vitamin deficiencies Several of the deaths observed in our Clinic occurred in such babies who were nearly moribund at the time they were first seen by a physician Although it is probably true that the Jarisch Herxheimer reaction occurs in infants with early congenital syphilis in the same proportion of cases about 50 per cent as in the early acquired disease this is characterized usually by fever alone It is at the present time impossible to say with certainty that fatal Herxheimer reactions do not occur in syphilitic infants following the institution of penicillin treatment but it is our impression that the fatalities which we have seen have been in infants who would probably have expired within a few days regardless of treatment of any kind the majority died after penicillin treatment had been completed We feel that syphilotherapy as described in the first paragraph of this section should be instituted promptly in any child with proven congenital syphilis and that the mortality rate would be further increased by withholding such treatment Of even greater importance than immediate syphilotherapy however is the need for these infants to have the benefit of expert and continuous pediatric care

Penicillin in Late Congenital Syphilis

As in the acquired disease results of penicillin therapy or any other type of treatment have been less striking in congenital syphilis of more than two years duration than in the earlier stages of the disease As a matter of fact several of the manifestations of late congenital syphilis are more discouraging than those of late acquired syphilis with the possible exceptions of primary optic atrophy and Charcot joints The most important of these is interstitial keratitis This condition is most frequent between the ages of 5 and 15 It may involve one eye only at the outset but almost invariably the second eye is affected sooner or later The condition begins as a diffuse keratitis and is followed by vascularization and corneal clearing as a rule whether or not treatment is given Spontaneous resolution may be so complete as to require a slit lamp examination to detect the ghost vessels in the cornea at this time The other characteristic and the most discouraging one is that recurrences are the rule These are attacks of iritis the cornea being involved only secondarily The recurrences are affected likewise little if at all by treatment Since no or only a few *T pallida* are present in these corneas the treponemicidal agent penicillin would be expected to have

little, if any, effect on this condition, and such has been the experience of workers in the field Penicillin combined with fever therapy probably represents the best treatment at present available, but all too frequently the process appears to be entirely unaffected by it[1]

Bilateral hydrarthroses, usually involving the knees (Clutton s joints), likewise appear to respond little, if at all, to penicillin treatment or to combined penicillin fever therapy

Lesions of benign late and visceral congenital syphilis respond as well to penicillin as in acquired late syphilis The antibiotic should be given in adult dosages of 3 to 6 million units

For reasons not at all understood syphilitic involvement of the cardio vascular apparatus to the extent of producing aneurysm or aortic insufficiency is extremely unusual in late congenital syphilis Although it may occur rarely, we have not treated a case with penicillin, nor does the current literature contain reports on this topic It is unlikely how ever, that penicillin would be either more or less effective than in cardio vascular disease due to acquired syphilis

Neurosyphilis in children is not infrequent, and all diagnostic types are encountered With one possible exception, vascular or meningo-vascular syphilis with sudden onset of focal symptoms, symptomatic neurosyphilis in children probably is diagnosed less promptly than is the case with adults In the case of juvenile paresis, for example, the child s behavior patterns must become profoundly altered before most parents suspect anything out of the ordinary is happening Frequently a child will fail to advance in school for 2 or 3 successive years or become involved with the authorities before it is suspected that something may be seriously wrong The adult on the other hand, usually has behavior patterns which are recognized by his intimates, when he begins to behave or react emotionally in an unusual manner, the changes are noted promptly by his family, as a rule, and medical attention obtained An additional factor in this regard is that most practitioners are far less apt to suspect neurosyphilis in a child than in an adult because of the asso ciation of syphilis with overt promiscuous, sexual activity Because of these factors the general end results in patients with juvenile paresis probably are inferior to results obtained in adults with a given type of treatment The psychoses have been present longer more central nervous system tissue has been irreparably destroyed and penicillin, like other methods of therapy, can only attack the treponemes present and at best arrest the process On the other hand children with paresis tabo paresis, tabes dorsalis or diffuse meningovascular syphilis, in whom the

diagnosis has been established early should benefit from penicillin or combined fever penicillin treatment to the same degree as adults suffering from *symptomatic acquired neurosyphilis* Since most of these children are in their teens adult dosages should be used 10 to 20 million units in 1 to 25 days and the remarks on treatment in acquired neurosyphilis are in general applicable here The more severe types paresis and tabes dorsalis should receive the benefit of fever plus penicillin

We feel that the really effective attack on these late types of congenital syphilis is the preventive one The penicillin treatment of the pregnant syphilitic woman and the treatment of children with congenital syphilis prior to the third year of life offer the best possibilities of avoiding these recalcitrant late manifestations Once they have appeared much damage has been done already and for some of them at least e g interstitial keratitis no methods of treatment at present available may be effective

Résumé of Treatment Schedules and Recommended Post Treatment Procedures

Penicillin treatment represents a distinct advance over older methods *of syphilotherapy for two main reasons* The antibiotic is essentially non toxic and schedules of treatment may be compressed into a practicable period of time Although treatment failures occur in approximately 10 per cent of patients with early syphilis careful and prolonged follow up studies should neutralize this disadvantage

Two general types of penicillin treatment are in use at the present time In patient therapy probably is destined to be largely discarded except in patients already hospitalized for other reasons in those with late cardiovascular or neurosyphilis in patients requiring supplementary induced fever therapy and in pregnant syphilitic women For most types of early and late syphilis, *brief ambulatory schedules of syphilotherapy* should be entirely adequate Preparations are available which will maintain treponemicidal serum levels of penicillin G for from 24 to 100 hours after a single intramuscular injection thus permitting the use of schedules involving daily or triweekly administration There is some evidence that the addition of *heavy metal chemotherapy* to such schedules may increase further the final incidence of cure in early syphilis

Except in gumma of the larynx neurosyphilis and possibly in cardiovascular syphilis the Jarisch Herxheimer reaction (therapeutic shock) probably may be safely disregarded

In Table II are summarized our current opinions as to the appropriate

TABLE II

Recommended Treatment Schedules for Various Types of Early and Late Acquired and Congenital Syphilis

Diagnosis	In Patient Therapy	Ambulatory Treatment
Early infectious acquired syphilis with or without complications including early neurosyphilis	50 000 100 000 units of penicillin in aqueous solution every 3 hours for 8 10 days 1 daily injection of 600 000 units (2 c c) of POB or POP for 10 injections or triweekly injections of 600 000 units (2 c c) of procaine penicillin with aluminum monostearate for 2 3 weeks	One daily injection of 600 000 units (c c) of POB or POP for 10 days triweekly injections of 600 000 units (2 c c) each of procaine penicillin with aluminum monostearate for 2 3 weeks
Early and late latent acquired syphilis	50 000 100 000 units of penicillin in aqueous solution every 3 hours for 3 6 days 1 daily injection of 600,000 units (c c) of POB or POP for 6 10 days 8 injections of 600,000 units (c.c) 3 days apart of procaine penicillin with aluminum monostearate	One daily injection of 600 000 units (2 c c) of POB or POP for 6 10 days 8 injections 3 days apart of 600,000 units (2 c.c) of procaine penicillin with aluminum monostearate
Late acquired syphilis		
Benign late osseous and visceral syphilis	50 000 100 000 units of penicillin in aqueous solution every 3 hours for 8 10 days 1 daily injection of 600 000 units (2 c c) of POB or POP for 8 10 days 8 injections of 600,000 units (2 c.c) 3 days apart of procaine penicillin with aluminum monostearate	One daily injection of 600 000 units (2 c c) of POB or POP for 10 days 8 injections of 600,000 units (2 c.c) 3 days apart of procaine penicillin with aluminum monostearate

TABLE II—Continued

Diagnosis	In Patient Therapy	Ambulatory Treatment
Cardiovascular syphilis	As for benign late syphilis	
Neurosyphilis		
Asymptomatic late or early	As for early infectious or benign late syphilis	
Acute syphilitic meningitis	As for early infectious syphilis	
Diffuse meningovascular syphilis	As for benign late syphilis	
Gumma of brain or spinal cord	As for benign late syphilis	
Vascular neurosyphilis	As for benign late syphilis	
Nerve deafness due to syphilis	As for benign late syphilis induced fever optional	
Erb s spastic paraplegia	As for early infectious or benign late syphilis induced fever optional	
General paresis	Induced fever is mandatory 50,000-100,000 units of penicillin in aqueous solution every 3 hours beginning with the first malarial paroxysm or hypertherm treatment continued for 100-odd injections injections of 600 000 units (1 c.c.) of procaine penicillin with aluminum monostearate tri weekly throughout febrile period daily injections of 600,000 units (c.c.) of POB or POC throughout febrile period	
Taboparesis		
Tabes dorsalis		
Syphilitic primary optic atrophy		

In Table II are summarized our current opinions as to the appropriate

TABLE II

RECOMMENDED TREATMENT SCHEDULES FOR VARIOUS TYPES OF EARLY AND LATE ACQUIRED AND CONGENITAL SYPHILIS

DIAGNOSIS	IN PATIENT THERAPY	AMBULATORY TREATMENT
Early infectious acquired syphilis with or without complications including early neurosyphilis	50 000 100 000 units of penicillin in aqueous solution every 3 hours for 8 10 days 1 daily injection of 600 000 units (2 cc) of POB or POP for 10 injections or triweekly injections of 600 000 units (2 c.c) of procaine penicillin with aluminum monostearate for 2 3 weeks	One daily injection of 600 000 units (2 cc) of POB or POP for 10 days triweekly injections of 600,000 units (2 cc) each of procaine penicillin with aluminum monostearate for 3 weeks
Early and late latent acquired syphilis	50 000 100 000 units of penicillin in aqueous solution every 3 hours for 3 6 days 1 daily injection of 600 000 units (cc) of POB or POP for 6-10 days 8 injections of 600,000 units (cc) 3 days apart of procaine penicillin with aluminum monostearate	One daily injection of 600 000 units (2 cc) of POB or POP for 6-10 days 8 injections 3 days apart of 600 000 units (2 cc) of procaine penicillin with aluminum monostearate
Late acquired syphilis		
Benign late osseous and visceral syphilis	50 000 100 000 units of penicillin in aqueous solution every 3 hours for 8 10 days 1 daily injection of 600 000 units (2 cc) of POB or POP for 8 10 days 8 injections of 600,000 units (2 cc) 3 days apart of procaine penicillin with aluminum monostearate	One daily injection of 600 000 units (2 cc) of POB or POP for 10 days 8 injections of 600,000 units (2 c.c) 3 days apart of procaine penicillin with aluminum monostearate

and inspection of the skin and mucous membranes should be done at each visit If the pretreatment lumbar puncture yields normal fluid it should be rechecked between one and two years after treatment If positive prior to therapy the cerebrospinal fluid should be examined every 6 months until it has become negative In the event of clinical relapse a rising serological titer or one still high after one to two years observation or if the cerebrospinal fluid fails to become inactive promptly retreatment with or without induced fever should be seriously considered

In patients with cardiovascular and late acquired or congenital neurosyphilis follow up visits may be less frequent as a rule It is our policy to see the patients with cardiovascular syphilis every 3 months the first year and to then follow them every 6 to 12 months or at whatever intervals the cardiac status will permit Patients with neurosyphilis should have lumbar punctures on each three monthly visit during the first year if the fluid before treatment was active if the activity is still present 6 to 12 months after the original treatment further syphilotherapy should be given So long as the fluid becomes and remains inactive we do not retreat unless there is definite clinical evidence of progression Paretics tabetics and patients with primary optic atrophy must be individualized as regards follow up to the same extent as patients with cardiovascular involvement In general we see each of these patients 4 times the first year and then every 6 months Each case must be evaluated in terms of the patient s particular need for medical attention but it is our feeling that little in the way of important changes for the worse will be missed if these follow up schedules are adhered to

Pregnant syphilitic women who have received penicillin in the past either during a previous pregnancy or during a nonpregnant interval should be followed intensively with complete examination of skin and mucous membranes and titered serological tests at monthly intervals throughout all subsequent pregnancies In the event of clinical relapse reinfection or a rising or a consistently high serological titer further penicillin treatment should be given immediately There is no justification for temporizing when there is a likely possibility of a syphilitic infant On the other hand if the mother remains clinically well during subsequent pregnancies if she remains seronegative or seroresistant in low and constant titer and especially if a healthy baby resulted from her last pregnancy there is strong evidence to show that her subsequent children will be non syphilitic in the absence of further maternal syphilotherapy

TABLE II—Continued

Diagnosis	In Patient Therapy	Ambulatory Treatment
Prevention of prenatal syphilis by treatment of the pregnant woman	As for early infectious syphilis	
Early or infantile congenital syphilis	400,000 units per kilogram of body weight divided into 10 12 aliquot doses of POB or POP or 5-6 aliquot doses of procaine penicillin with aluminum monostearate given at or 3 day intervals	
Late congenital syphilis		
Benign late osseous or visceral syphilis	As for benign late acquired syphilis	As for benign late acquired syphilis
Interstitial keratitis Clutton's joints etc	Induced fever mandatory Penicillin treatment as for primary optic atrophy Metal chemotherapy may be tried	
Neurosyphilis	As for corresponding types of acquired neurosyphilis	

penicillin treatment for the various diagnostic categories of syphilitic disease Crystalline penicillin G is understood in all references to the antibiotic The slowly absorbed penicillin preparations in the last two columns, which yield prolonged serum concentrations following a single intramuscular injection include penicillin in peanut oil beeswax (POB), procaine penicillin in sesame or peanut oil (POP) and procaine penicillin in water with or without the addition of aluminum monostearate All are marketed in concentrations of 300,000 Oxford units per c c of suspension

Follow-up for patients with early acquired or congenital syphilis should be once a month for the first year every 3 months the second year and then once or twice a year indefinitely Serological tests, titered,

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June 1 1949

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